Management Conundrums and Quandaries in Women’s Health

Session Objectives

1. Review recent evidence related to the treatment of osteoporosis in women.
2. Examine menopause management for the difficult-to-treat woman.
3. Manage conundrums with LARCs.

Conflicts of Interest

- I have no conflicts of interest and nothing to disclose.

What’s NEW in Osteoporosis?

- Approximately 10 million persons in the United States have osteoporosis and another 44 million have osteopenia, placing them at increased risk for fracture (Burkett & Eddy, 2017). Bone densitometry: Performance, interpretation, and clinical application. Downloaded from NPWomensHealthcare.com.
- 1 in 3 women will have a fragility fracture by the age of 50.
- 1 in 2 women will have a fragility fracture in their lifetime, an incidence greater than that of myocardial infarction, stroke, and breast cancer combined.

What is involved in the osteoporosis work-up?

- According to guidelines published by the American Association of Clinical Endocrinologists and the American College of Endocrinology in 2016, all postmenopausal women aged 50 years or older should undergo clinical assessment for osteoporosis and fracture risk, including:

  - A detailed history and physical examination,
  - Check for prior non-traumatic fractures,
  - Low body weight (<127 lb),
  - Family history of osteoporosis and/or fractures (esp mother or father),
  - Early-onset menopause,
  - Smoking,
  - Excessive alcohol intake (what is “excessive”? GUESS!)
  - (23 drinks/day)
  - HCPs should also assess each woman’s risk factors for falling,
  - Height loss or kyphosis
  - HOW MUCH height loss?
  - >1.5”

What is involved in the osteoporosis work-up?


- The AACE/ACE also recommends lateral spine imaging with standard radiography or vertebral fracture assessment (VFA).
- DXA can take images of vertebral morphology (T7-L4) enabling VFA with extremely low radiation doses to patients.
- Recognition of vertebral fracture may change diagnostic category, increase estimate of fracture risk, or change treatment decisions.

Beyond pain, why are vertebral fractures important?

- 2/3 vertebral fractures are asymptomatic, but they are not BENIGN.
- 8% of lung function is lost with each vertebral fracture.

Who are candidates for BMD measurement?


Who should be sent for BMD measurement?

(1) all women aged 65 years or older, as well as younger postmenopausal women who
(2) have a history of fracture without major trauma,
(3) are on long-term systemic steroids,
(4) have radiographic osteopenia, or
(5) have clinical risk factors for osteoporosis.

What are the major risk factors for osteoporosis fractures?

- Low Calcium diet
- Low Vitamin D Level
- Being very thin
- Immobility
- Smoking
- Excessive ETOH use
- High risk of falling

> age 65

2 or more of any of these = HIGH RISK
How much calcium and Vitamin D do women with low BMD need?

Recommendations for optimal treatment should include daily intakes of 1000 mg/day to 1200 mg/day of calcium and a minimum of 1000 IU to 2000 IU of vitamin D3, along with regular monitoring of serum 25-hydroxyvitamin D and parathyroid hormone (PTH) levels.

What labs are recommended to determine whether osteoporosis might be secondary to another cause?


- CBC,
- CMP,
- 25-hydroxyvitamin D,
- PTH,
- bone-specific alkaline phosphatase,
- 24-hour urine collection for calcium and creatinine.

How does estrogen work to help prevent osteoporosis?

- Does it......
- A. inactivate osteoclasts
- B. increase the growth and number of osteoblasts
- C. enhance the binding calcium and vitamin D to bone matrix
- D reduce the number of osteoclasts

What changes, if any, do you recommend in Stella’s medication regimen?

CASE 1: Osteoporosis Management

Stella Smith is 72 years old and has a T score of -2.8 at her spine and -2.5 at her hip. She also has severe acid reflux for which she takes Nexium to keep the reflux in check. She says “taking calcium really aggravates my stomach and makes me constipated”.

Nexium may reduce stomach acid and reduce absorption of calcium carbonate, contributing to osteoporosis.

Continue Nexium if needed for reflux.
Change to calcium citrate – does not require an acidic environment for absorption.
Continue Vitamin D as indicated by 24 hydroxyvitamin D level
Switch from Fosamax to Reclast or Prolia.
Add a low dose of magnesium to reduce the constipating effects of calcium (160-250 mg)

In what situation should a woman NOT take magnesium supplements? If she has:
- A. impaired liver function
- B. chronic kidney disease
- C. hypertension
- D. triglycerides >300 mg/dL

- B. chronic kidney disease
Let's talk about bisphosphonates! Cosman et al. (2014).


Research has demonstrated that which of the following oral bisphosphonates increases BMD and decreases fracture risk at the hip and the spine?

• 1. Boniva/Ibandronate
• 2. Fosamax/Alendronate
• 3. Actonel/Risedronate sodium

A. 1 C. 3, 4
B. 2, 3 D. 1, 2, 3

B. 2, 3 (Boniva is indicated for increase in BMD & reduction in the incidence of vertebral fractures only).

Who should be treated with pharmacotherapy? Camacho et al., 2016

The AACE and NOF strongly recommend pharmacotherapy for persons with:

• Osteopenia and a history of a fragility fracture of the spine or hip;

• A T-score of −2.5 or lower in the spine, femoral neck, total hip, or distal one-third radius; or

• A T-score between −1.0 and −2.5 in the spine, femoral neck, total hip, or distal one-third radius and a FRAX 10-year risk of hip fracture equal to or greater than 3% or a FRAX 10-year risk of a major osteoporosis-related fracture equal to or greater than 20%.

FRAX® is NOT perfect!

FRAX® predicts the 10-year probability of hip fracture and major osteoporotic fracture. FRAX® underestimates future fracture risk as it reports risk for only hip and major fractures, which comprise approximately half of all fragility fractures.

FRAX® also underestimates risk in patients with:

• multiple osteoporosis-related fractures,

• recent fractures,

• lumbar spine BMD much lower than femoral neck BMD,

• those with secondary osteoporosis, and

• those at increased risk of falling (Camacho et al., 2016).

Which drugs are considered “first line” for osteoporosis?

• Alendronate, risedronate, zoledronic acid, and denosumab—have evidence for “broad spectrum” anti-fracture efficacy and are considered first line options in most cases (Camacho et al. 2016).

• Patients with moderate fracture risk, but no fragility fractures, can be started on an oral agent—that is, alendronate or risedronate (Camacho et al. 2016).

What’s NEW in Osteoporosis? Case 2:

Janice is a 56 year old white female, 5’6” tall, 113 pounds and works as a computer analyst. She takes the following medications daily: Symbicort, Singulair, and Levothyroxine. She walks for about 45 minutes daily, does not drink or smoke, and follows a vegan diet. She started on Zoledronic Acid (Reclast) 3 years ago when her first DEXA demonstrated a femoral neck T score of -2.8 and lumbar spine of -2.5. Janice had another DEXA scan today and her T score is now -2.5 at the femoral neck and -2.1 at the lumbar spine.
Case 2: What would you do NEXT regarding her osteoporosis medication management?

• A. Start her on a bisphosphonate “holiday”.
• B. Change her to Prolia.
• C. Change her to Forteo.
• D. Give her another 3 years of Reclast

How long should bisphosphonate therapy be continued?

• In 2015, the American Society of Bone and Mineral Research (ASBMR) examined fracture risk reduction as well as increases in BMD in 2 trials that explored long-term use of bisphosphonate in the treatment of osteoporosis:
  • Fracture Intervention Trial Long-Term Extension (FLEX)
    • Received alendronate for 10 years
  • Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) study extension
    • Received Zoledronic Acid for a total of 6 years.

FLEX Trial

• This study was conducted among women who had previously received alendronate for 5 to 10 years during the Fracture Intervention Trial (FIT). Participants in the FLEX study were randomly assigned to receive alendronate (either 5 or 10 mg/day) or matching placebo during the next 5 years, in order to evaluate the effects of continuing or discontinuing alendronate treatment on bone mineral density and biochemical markers of bone turnover.
  • 1099 participants; Primary outcome measure was total hip bone BMD; Secondary outcome measure was BMD of femoral neck, trochanter, and spine.

What about Oral Bisphosphonate-Related Osteonecrosis of the Jaw? (BRONJ)

• How many cases of BRONJ occurred in the 662 women who used Fosamax for 10 years in the FLEX Trial?
  • A. 1
  • B. 4
  • C. 11
  • D. 17
  • NO cases of Oral Bisphosphonate-Related Osteonecrosis of the Jaw even after 10 years of use in the FLEX Trial.
• Even long-term use carries little risk of BRONJ
Conclusions from FLEX and HORIZON E1

• A hip T-score between -2 and -2.5 in FLEX and below -2.5 in the HORIZON E1 predicted a beneficial response to continued therapy (Goldstein, 2015).


• Risk factors for continued therapy include continued low T-score, older age, and any previous fracture – especially if that fracture occurred during therapy (Adler et al., 2015; Goldstein, 2015).

Conclusions from FLEX and HORIZON (Adler, et al., 2015).

• The ASBMR did not find the risk of BRONJ to be increased with prolonged therapy.

• The ASBMR did find the risk of atypical fracture to increase with length of therapy. However, such rare events are outweighed by risk reduction of vertebral fracture risk reduction in high-risk patients.

What is the PURPOSE of a drug holiday?

• On October 13, 2010 the FDA sent out a notice to HCPs: FDA Drug Safety Communication: Safety update for osteoporosis drugs, bisphosphonates, and atypical fractures and identified an association between atypical femoral fracture (AFF) and bisphosphonate use. The risk of AFF was identified as <1%.

• A “Drug Holiday” was suggested to reduce the risk of rare side effects, including atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ).

Drug Holiday

• If a drug holiday is recommended for a woman on a bone-building drug, what is the longest it should last?
  • A. 1 year
  • B. 2 years
  • C. 3 years
  • D. 5 years

• In women who do not have high fracture risk after 3-5 years of bisphosphonate therapy, a drug holiday limited to 2 years is recommended (Adler et al., 2015).

What is the PURPOSE of a drug holiday?

• The risk of AFF, which has been estimated to double with bisphosphonate treatment longer than 3 years, appears to decline with discontinuation of the drug, while the drug’s anti-resorptive effects remain persistent, hence the potential benefit of a “drug holiday.”

• But drug holidays are only appropriate for LOW RISK women.

• Many patients, as well as their HCPs, do not seem to understand “drug holiday” related to bone-building drugs.
What is the PURPOSE of a drug holiday?

• “Osteoporosis medication use among people who have already sustained hip fractures — and are therefore at a very high risk of re-fracture — has in fact declined significantly, from 40% in 2002 to only 21% in 2011” *(J Bone Miner Res. 2014;29: 1929-1937).*

So what happens during a “drug holiday”?


• A second extension of the HORIZON Trial (E2), in which women on Zoledronic Acid (ZOL) (Reclast) for 6 years in the first extension were randomized to either Zoledronic Acid (ZOL) (Reclast) or placebo for 3 additional years (190 women were randomized to Z9 (n=95) and Z6P3 (n=95)) (for a total of 9 continuous years of treatment with Reclast).

HORIZON Trial (Extension 2 – E2)

• The primary endpoint was change in total hip BMD at year 9 vs. year 6 in Z9 compared with Z6P3.
• Secondary endpoints included fractures, bone turnover markers (BTMs), and safety.

HORIZON Trial (Extension 2 – E2): RESULTS

• From year 6 to 9, the mean change in total hip BMD was 0.54% in Z9 vs. 1.31% in Z6P3 (difference 0.78%; 95% confidence interval [CI]: 0.37%, 1.93%; *p* ≤ 0.183).
• BTMs showed small, non-significant increases in those who discontinued after 6 years compared with those who continued for 9 years.
• The number of fractures was low and did not significantly differ by treatment.
• While generally safe, there was a small increase in cardiac arrhythmias (combined serious and non-serious) in the Z9 group but no significant imbalance in other safety parameters.

HORIZON Trial (Extension 1 & 2 – E1 & E2): Conclusions

• The first 3-year extension of HORIZON (E1) showed that the continuation of ZOL treatment from 3–6 years resulted in maintenance of BMD, a decrease in vertebral fractures, and a modest reduction in bone turnover markers (BTMs) vs. discontinuation with no evidence of difference in the incidence of non-vertebral fracture.
• The second 3-year extension (HORIZON E2) suggest almost all patients who have received six annual ZOL infusions can stop medication for up to 3 years with apparent maintenance of benefits.
What is the Risk of Bisphosphonate-Related Osteonecrosis of the Jaw?

• Take a GUESS! In five studies of Reclast lasting three years with a total of 5900 women, how many women developed bisphosphonate-related ONJ?
  • A. 1
  • B. 11
  • C. 101
  • D. 181
  • A. 1

What about Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ)?

• The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Trial found one case of osteonecrosis of the jaw (ONJ) in a patient with postmenopausal osteoporosis (OP) treated with 5 milligrams of zoledronic acid (ZOL) once yearly and one case in a patient receiving a placebo.

• The authors examined ONJ incidence in four additional clinical trials involving patients with osteopenia or osteoporosis who were treated with ZOL.

• To determine ONJ prevalence, an independent committee conducted a masked review of the clinical trials’ adverse events databases for cases meeting predefined criteria for ONJ.

Results and Conclusions

• 5,903 patients received ZOL in the five clinical trials.

• The results of the four additional clinical trials revealed no further cases of ONJ.

• In the clinically diverse group of 5,903 patients who received ZOL in five clinical trials, ONJ incidence was less than one in 14,200 patient treatment-years.

• Clinical Implications:
  • Occurrences of ONJ are rare in patients with osteoporosis who are receiving ZOL.

Menopause: It’s a thin line between love and homicide

Menopause Management for the Difficult-to-Treat Woman: Troubleshooting Hormone Therapy

QUESTION!!

• Which of the following contains the MOST estrogen?
  • A. 2 mg Estrace tablets
  • B. 1.25 mg Premarin tablets
  • C. 0.1 mg Vivelle patch
  • D. Lo-Lestrin 10 mcg
  • E. All are equivalent
  • E. All are equivalent

2 mg Estrace = 1.25 mg. Premarin = 0.1 mg Vivelle patch = 10 mcg EE…that is why blood levels of estrogen will be similar regardless of type of estrogen administered in ET/HT
Estrogens in Oral Contraceptives and ET/HT

• OCPs: Ethinyl Estradiol (EE)
• HT/ET: conjugated equine estrogens (CEE), piperazine estrone sulfate, esterified estrogens, oral micronized E2, and transdermal E2, and estradiol acetate
• Regardless of the type of estrogen administered, blood levels of estradiol will be similar...as long as you know equivalent doses!

CASE 3: Persistent Hot Flashes
Susan, 45 years old, went into menopause 9 months ago. Her PCP started her off on a generic estradiol patch 0.05 mg with micronized progesterone days 1-14 of each month. She didn’t like the big patch because of all the adhesive it left on her skin and her hot flashes continued. Her PCP changed her to Premphase; hot flashes continued. He changed her to Premarin 1.25 mg daily and Provera 10 mg days 1-14 of each month. Now she is seeing you and says “Please, I’m desperate for some help with these hot flashes!”

It’s all about Sex Hormone Binding Globulin
An organ’s response to HT is governed by a number of factors, including
1. the availability of free estrogen and free testosterone - only “free” forms of hormones can attach to receptors and exert hormonal effects; determined by the (1) route and (2) type of HT,
2. the concentration of estrogen - (3) determined by adjusting the dose,
3. the number of available estrogen receptors - (4) activated by the addition of progestins.

Progestins in Oral Contraceptives and HT

• 17-acetoprogesterone → Pregnanes (medroxyprogesterone acetate: MPA/Provera and Megestro/Megace)
• 19-nortestosterone → Estranes (norethindrone, norethindrone acetate, ethynodiol diacetate, lynestrenol, and norethynodral) and → Gonanes (norgestrel, levonorgestrel, norgestimate, gestodene, and desogestrel)
• Drospironone

Pharmacologic Differences: All Hormonal Preparations are not Equal
• The bioavailability of free estrogen is determined primarily by its binding to Sex Hormone Binding Globulin (SHBG).
The greater the amount of SHBG stimulated, the more estrogen is bound, thus producing less free estrogen.
Sex Hormone Binding Globulin

• Sex Hormone Binding Globulin (SHBG), is a hepatic protein that binds tightly to dihydrotestosterone (DHT), testosterone and estradiol, transporting them in the blood in a metabolically inactive form.

• The amount of SHBG in a patient's blood is affected by sex and age, and increased or decreased by testosterone or estrogen production. It can also be affected by diseases and conditions such as obesity, liver disease, and hyperthyroidism or hypothyroidism.

Increased SHBG levels may be seen in:
• Liver disease
• Hyperthyroidism
• Eating disorders (anorexia nervosa)
• Corticosteroids or estrogen use (hormone replacement therapy and oral contraceptives)

Decreases in SHBG are seen with:
• Obesity
• Polycystic ovary syndrome
• Hypothyroidism
• Androgen (steroid) use
• Cushing disease
• Hypogonadism

HT compounds stimulate the production of SHBG differently. A study by Nachtigall et al. (2000) found that more free estrogen is available in some compounds that others, even at clinically equivalent doses, because of variations in stimulation of SHBG:

<table>
<thead>
<tr>
<th>Compound</th>
<th>SHBG Stimulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05 mg transdermal</td>
<td>12%</td>
</tr>
<tr>
<td>1 mg 17 B estradiol</td>
<td>45%</td>
</tr>
<tr>
<td>0.625 mg CEE</td>
<td>100%</td>
</tr>
</tbody>
</table>

Treatment of Hot Flashes

Adding a progestin may help to further reduce hot flashes and night sweats by activating estrogen receptors.

Adding androgens may also be helpful. The addition of 2.5 mg methyltestosterone to 1.25 mg esterified estrogen (Estratest) decreased SHBG (from +46 to +24 mcg DHT bound/DL) resulting in more free, and therefore, bioavailable estradiol and testosterone (Simons et al, 2002). The addition of testosterone to estrogen therapy may also be useful in increasing BMD.

This is not a preferred strategy due side effects and negative effect on lipids.

Androgenic progestins (norgestrel; levonorgestrel) have an anabolic effect similar to testosterone (preferred).

The clinical message is this:

For women who are non-responsive to traditional, adequate doses of oral hormone therapy, consider changing the type of oral estrogen, the route of administration, or the addition of an androgen before increasing the HT dose.

Non-hormonal medications may be used along with HT to reduce vasomotor symptoms.
### Non-Hormonal Medications for Menopause Management

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Range</th>
<th>Starting Dose</th>
<th>Titration Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine salt</td>
<td>7.5 mg/d</td>
<td>Single dose</td>
<td>No titration needed</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10-25 mg/d</td>
<td>Start with 10 mg/d</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>10-20 mg/d</td>
<td>Start with 10 mg/d</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10-20 mg/d</td>
<td>Start with 10 mg/d</td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>100-150 mg/d</td>
<td>Start with 25-50 mg/d and titrate up by that amount each day</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5-150 mg/d</td>
<td>Start with 37.5 mg/d</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900-2,400 mg/d</td>
<td>Start with 300 mg at night, then add a separate dose of 300 mg in the morning (start at 100 mg if concerned about sensitivity)</td>
<td></td>
</tr>
</tbody>
</table>

### Remember
Symptomatic control of menopausal hot flashes and night sweats does not confirm adequate estrogrenization of all target tissues.

About 30-40% of women on ET/HT will still have evidence of atrophic vaginitis (easily diagnosed by elevated vaginal pH).

### Progestins for Hot Flash Control

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Range</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral MPA/Provera</td>
<td>10-20 mg/d</td>
<td>50-80% effective</td>
</tr>
<tr>
<td>Injectable DMPA</td>
<td>150 mg/1-2 mo.</td>
<td>85% effective</td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>2.5 mg q D</td>
<td>75-80% effective</td>
</tr>
<tr>
<td>Micronized progesterone</td>
<td>300 mg q HS</td>
<td>Percentage unreported</td>
</tr>
</tbody>
</table>

### Case 4: Low libido

- Angie Miller is 55 and is on Prempro 0.45/1.5 mg. She complains of decreased libido ever since going into menopause and starting this medication. She has been in menopause for 3 years. She has no pain with intercourse; she just has little desire and has a great deal of difficulty achieving an orgasm. This never used to be a problem for Angie.
- What is the physiologic basis for decreased libido after menopause? Using commercially manufactured products, create a plan for Angie.

- Decreased androstenedione production by the ovaries -> decreased testosterone. Consider changing to ClimaraPro. More androgenic. Less SHBG with patch estrogen.

- Angie says “that just didn’t work”; “I don’t think I have any testosterone in my body”. If you wanted to measure hormone levels to determine the amount of circulating androgen Angie has, what would you order?

  - Free testosterone level

- What other manufactured hormone options do you have to provide her with exogenous testosterone?
  - Estratest HS or Estratest
  - How will you know when her testosterone level is adequate?
  - You can retest to be sure she is in the normal range; if still no libido, search for other causes.
CASE 5: Bleeding Irregularities with Cu-IUD Use

Sally, age 28, is a healthy G2P0A0L0 who has had a Cu-IUD since her 6 week check-up 6 months ago. She weaned her daughter after a month of breastfeeding, and is taking no medication beyond her multivitamin. She is worked-in today for complaints of irregular bleeding with her IUD. Ever since she got this IUD she has had unpredictable BTB and spotting that is sometimes light, sometimes heavy, and lasting as long as 10 days. She has no pain, D/C, or new partners.

Assume you evaluated this bleeding and could find no abnormalities to account for it. Answer the following questions in your groups:

- How long should women expect to have irregular bleeding after a Cu-IUD is inserted?
  - 3-6 months of light, heavy, or prolonged BTB & spotting.
- Is there anything that we can give or suggest to Sally that will help this bleeding? (What do you do in your practice?)

What does the research evidence suggest?

Nine studies have examined the use of various oral NSAIDs for the treatment of heavy or prolonged menstrual bleeding among Cu-IUD users and compared them to either a placebo or a baseline cycle.

- suprofen (Clin Exp Obstet Gynecol 1987;14:41–4, 106) [Neither available in USA].
- All but one NSAID study (Contracept Deliv Syst 1982;3:115–9) demonstrated statistically significant or notable reductions in mean total menstrual blood loss with NSAID use.
- Use for 5-7 days to control bleeding.

One study among 19 Cu-IUD users with heavy bleeding suggested that treatment with oral tranexamic acid (Lysteda) can significantly reduce mean blood loss during treatment compared with placebo (Br J Obstet Gynaecol 1983;90:78–83.).
CASE 6: Bleeding Irregularities with LNG-IUS Use

Sally, age 28, is a healthy G2T2P0A0L0 who has had a LNG-IUS since her 6 week check-up 6 months ago. She weaned her daughter after a month of breastfeeding, and is taking no medication beyond her multivitamin. She is worked-in today for complaints of irregular bleeding with her IUD. Ever since she got this IUD she has had unpredictable BTB and spotting that is sometimes light, occasionally heavy, and lasting as long as 10 days. She has no pain, D/C, or new partners.

 assumed you evaluated this bleeding and could find no abnormalities to account for it. Answer the following questions in your groups:

- How long should women expect to have irregular bleeding after a LNG-IUS is inserted?
  - 3-6 months of light, heavy, or prolonged BTB & spotting.

- How would you manage this issue in your practice?
  - If clinically indicated, consider an underlying gynecological problem, such as LNG-IUD displacement, an STD, pregnancy, or new pathologic uterine conditions (e.g., polyps or fibroids).
  - If an underlying gynecological problem is found, treat the condition or refer for care.
  - If bleeding persists and the woman finds it unacceptable, counsel her on alternative contraceptive methods, and offer another method if it is desired (Personally, I would try a few other things FIRST).

What medications have been used to decrease bleeding with the LNG-IUS? (Sahmay, S. (2011). How to manage irregular bleeding or spotting after LNG-IUS insertion. Medical Forum International, 16(4), 14-18.)

- Prostaglandin synthase inhibitors decrease menstrual bleeding by 50%; most studies have shown that NSAIDs are effective therapy for irregular bleeding and pain related to the use of IUDs.
  - Mefenamic acid is the most commonly studied agent, the usual dosage being 500 mg three times a day. The dosage for naproxen is 500 mg twice a day during the bleeding or spotting period. The dosage regimen for ibuprofen is 1200 mg per day in divided doses.
  - NSAIDs should be considered a first-line therapy for bleeding and pain associated with IUD use.

- Plasminogen activators are a group of enzymes that cause fibrinolysis (the dissolution of clots). Women with bleeding problems have high levels of plasminogen in their endometrium. Antifibrinolytics have been used as a first-line agent to treat menstrual bleeding problems for over 40 years in both the United Kingdom and Scandinavia. Antifibrinolytics are more effective than NSAIDS.


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What other options exist?

Tranexamic acid and LNG-IUS (Sahmay, S. (2012). How to manage irregular bleeding or spotting after LNG-IUS insertion. Medical Forum International, 16(4), 14-18.)

- Plasminogen activators are a group of enzymes that cause fibrinolysis (the dissolution of clots). Women with bleeding problems have high levels of plasminogen in their endometrium.


- Antifibrinolitics have been used as a first-line agent to treat menstrual bleeding problems for over 40 years in both the United Kingdom and Scandinavia. Antifibrinolitics are more effective than NSAIDS.
What does the evidence suggest?
Tranexamic acid (Lysteda) and LNG-IUS

- The usual dosage is 1300 mg PO 3 times a day.
- Typically, this dose is usually sufficient to treat irregular or heavy menstrual bleeding associated with IUD use.

What does the evidence suggest?
Progestosterone receptor modulators

- Progestosterone receptor modulators have shown benefit in treating women with unscheduled bleeding during use of a progestogen-releasing contraceptive implant.
- Mifepristone (RU486) is a well known progesterone receptor antagonist that has been shown to decrease breakthrough bleeding in DMPA and Norplant® users. Mifepristone causes downregulation of progesterone receptor B and upregulation of estrogen receptors. This receptor modulation leads to cessation of breakthrough bleeding.

How is mifepristone dosed in LNG-IUS users?

- The effect of mifepristone in 36 LNG-IUS users was studied by Lal et al. (2010). All were given mifepristone 100 mg at the time of LNG-IUS insertion and then at 30-day intervals for 3 months (total dose 400 mg). The results of the study indicated that mifepristone reduced the duration and episodes of intermenstrual bleeding/spotting in women using the LNG-IUS. This beneficial effect persisted in the mifepristone group for 3 months after the intervention had been stopped. It suggests that mifepristone may be used in women experiencing irregular bleeding/spotting with the LNG-IUS.

What about using estrogen to reduce endometrial atrophy and decrease bleeding?

- Randomized controlled trial of naproxen, estradiol, or placebo administered over the first 12 weeks of LNG-IUS use.
- There were 129 women randomized to naproxen (n=42), estradiol (n=44), or placebo (n=43).
- The naproxen group was more likely to be in the lowest quartile of bleeding and spotting days compared to placebo, 42.9% versus 16.3% (p=0.03). In the multivariable analysis, the naproxen group had a 10% reduction in bleeding and spotting days (RR_adj 0.90, 95%CI 0.84–0.97) compared to placebo. More frequent bleeding and spotting was observed in the estradiol group (RR_adj 1.25, 95%CI 1.17–1.34).

Conclusions:

- NSAIDs and tranexamic acid offer simple and effective therapies and should be considered as first-line therapy options in LNG-IUS-related bleeding/spotting and pain.
- Tranexamic acid is more effective than NSAIDs in decreasing bleeding. If bleeding is associated with pain, NSAIDs should be considered as first-line therapy.
- Tranexamic acid is suitable in cases with only bleeding/spotting, since it offers no pain relief.

Case 7: Pain with insertion

- Jaime is a 23 year old nulligravida who wants to use an IUD for contraception. Her APRN attempted to insert an IUD this afternoon but was unsuccessful. The APRN was unable to pass the sound due to Jaime’s tightly closed internal cervical os and Jaime’s associated pain level.
- What suggestions do you have for reducing the pain of insertion for Jaime and increasing the chance of a successful second attempt?
Pain and IUD Insertion
doi: 10.1093/humupd/dmt022

- Meta-analysis to evaluate strategies for pain management for IUD insertion.
- Seventeen studies were identified and included: 12 RCTs and one non-randomized study of pre-insertion oral analgesia, cervical priming and local anesthesia; one systematic review and one RCT on post-insertion analgesia and two non-randomized studies on non-pharmacological interventions.
- There was no conclusive evidence that any prophylactic pharmacological intervention reduces pain associated with IUD insertion. However, most of the regimens studied were adopted from hysteroscopy or abortion and effectiveness in specific subsets of women has not been studied adequately.

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What does the literature say about Misoprostol?

1. Tightly closed internal and/or external os

**Misoprostol, yes or no?**

- Internet survey with 2211 respondents
- 1905 (86%) reported providing IUDs to nulliparous women.
- 947/1905 (49.7%) reported using misoprostol
- 380 (40%) of 947 of misoprostol users reported using the treatment empirically with all nulliparous IUD insertions.
- Dose, route, timing varied widely
- Providers adopted based on “word of mouth” not medical literature (Ward, 2011)

**Misoprostol, yes or no?**

Even though RCTs show no benefit and more side effects these are studies of randomized nullips; may still be possible benefits with difficult cases.

Authors recommend 400 mcg two hours prior sublingual or 400 mcg three hours prior vaginal/buccal
Not first line due to lack of evidence

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https://www.pexels.com/photo/color-drugs-medicine-pills-415804/

Cochrane review that included 33 trials with 5710 participants total; 29 were published from 2010 to 2015. Studies examined lidocaine, misoprostol, NSAIDs, and other interventions.

- Lidocaine: meta-analysis showed topical 2% gel had no effect on pain at tenaculum placement (two trials) or on pain during IUD insertion (three trials). Other formulations were effective compared with placebo in individual trials. Mean score for IUD-insertion pain was lower with 4% lidocaine gel, 10% spray, and lidocaine and prilocaine cream (MD -1.96, 95% CI -3.00 to -0.92).
Pain and IUD Insertion: Misoprostol

- In meta-analysis, cramping was more likely with misoprostol (OR 2.64, 95% CI 1.46 to 4.76; four studies).
- A trial with nulliparous women found a higher score for IUD-insertion pain with misoprostol (median 46 versus 34).
- Pain before leaving the clinic was higher for misoprostol in two trials with nulliparous women (MD 7.60, 95% CI 6.48 to 8.72; medians 35.5 versus 20.5).
- In one trial with nulliparous women, moderate or severe pain at IUD insertion was less likely with misoprostol (OR 0.30, 95% CI 0.16 to 0.55) (Lopez et al., 2015).

Pain Medication & IUD Insertion

- Among multiparous women, mean score for IUD-insertion pain was lower for tramadol 50 mg versus naproxen 550 mg (MD -0.63, 95% CI -0.94 to -0.32) and for naproxen versus placebo (MD -1.94, 95% CI -2.35 to -1.53).
- The naproxen group was less likely than the placebo group to report the insertion experience as unpleasant and not want the medication in the future (Lopez et al., 2015).

Malposition statistics/risk factors

10% of IUDs are malpositioned

Risk Factors
- More common if adenomyosis suspected (OR 3.04; CI: 1.08-8.52) – possibly related to change in contractility of uterus
- Not associated with type of IUD, breastfeeding status, post-abortion or 6-9 week postpartum insertion
- Protective: prior vaginal delivery (OR 0.53; CI: 0.32-0.87) (Braaten, K. (2012). OBG Management Vol. 24, No. 8)

The IUD Shuffle - Movement After Insertion

- IUDs move up/down uterus after insertion (Shimon et al, 2014)
- Most commonly, IUDs shift towards fundus after insertion
  - This is particularly true in women with lower parity (Morales-Rosello 2005)
  - Around 2 of out 3 misplaced IUDs will move into proper position within 3 months without any intervention (Faundes 2000)
- Watchful waiting is a reasonable option
  - Can repeat Ultrasound in 3 months to re-assess position
  - May want to cover with backup contraception in mean-time

The Low-down on Low-down IUDs: Malposition and IUD Failure

- IUD not at fundus is at higher risk for expulsion (Petta, 1996)

Copper IUD:
- Odds ratio for pregnancy with intracervical insertion 13.93 (95% CI 4.13-48.96) --- Absolute risk increase of ~1-2% (Anteby, 1993)

LNG IUD:
- Intracervical versus fundal placement found no difference in failure between groups (Pakarinen, 2005)

So, What To Do With an IUD in The Lower Uterine Segment?

- First, it depends on symptoms
  - Removal and reinsertion may resolve pain or bleeding
- Second, it depends on type of IUD
  - LNG IUD
    - Protects just as well against pregnancy in lower uterine segment versus fundus; so, if no symptoms - let it be.
  - Copper IUD
    - May be less effective; best practice would be to replace
    - If replacement too costly, can advance with alligator forceps (if not in endocervical canal) (78% effective) (Braaten, 2012)
    - Even misplaced, still more effective than OCP's (Braaten, 2012)
Management Conundrums and Quandaries in Women's Health

• THANK YOU for sharing your practice expertise, insights and knowledge with the rest of us!
• Any last comments or questions??

THANKS FOR LISTENING