Every woman’s journey through rheumatic disease is unique, filled with twists and turns as life’s challenges come and go. Each week, rheumatology nurses, nurse practitioners, and physician assistants field challenging questions from women with rheumatic diseases about their unique issues, and they need to be able to properly and effectively communicate appropriate responses. This pocket guide includes a brief summary of evidence surrounding some of the most common—and challenging—questions that women are asking about rheumatic disease. We hope you find this guide useful for your professional development.
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What’s the connection between hormones and my disease?

Female hormones are a key player in the onset and disease course for many autoimmune and systemic inflammatory rheumatic diseases.

Several of the autoimmune and systemic inflammatory rheumatic diseases disproportionally affect females. For instance, females are 2-3 times more likely to develop rheumatoid arthritis (RA) and 9 times more likely to develop systemic lupus erythematosus (SLE) than men.\textsuperscript{1,2} On the other hand, some rheumatic diseases have a similar incidence between females and males, such as psoriatic arthritis (PsA), or affect men more frequently, such as gout and ankylosing spondylitis.\textsuperscript{3-6}
Beyond genes and environmental triggers, female sex hormones (e.g., estrogen, androgens, progesterone, and prolactin) may facilitate the development and disease course of some autoimmune and systemic inflammatory diseases, although their exact contribution is still not fully understood.\textsuperscript{2,7}

Both estrogen and prolactin are considered pro-inflammatory hormones, whereas androgens (e.g., testosterone) and progesterone are thought to be anti-inflammatory. These hormones interact with and modulate the immune response both directly and indirectly, but the effects vary with different types of immune-mediated disease.\textsuperscript{2,8}

For example, high levels of estrogen and progesterone have been shown to be protective against disease onset and activity in women with RA.\textsuperscript{7,9} Similarly, high estrogen states (e.g., oral birth control) have been associated with improvements in PsA disease activity.\textsuperscript{10} On the other hand, findings suggest higher levels of estrogen may be involved in the development and disease activity in women with SLE.\textsuperscript{2,7,8}

Understanding how levels and ratios of pro-inflammatory and anti-inflammatory sex hormones fluctuate throughout a woman’s life (menstruation, pregnancy, postpartum period, and menopause) can shed some light on why disease onset and activity for systemic inflammatory diseases may vary over time as well. We’ll talk more about these issues later in this pocket guide.
References


Why does my disease get worse during menstruation?

It has a lot to do with the rise and fall of hormones during the menstrual cycle.

During a women's reproductive years, the body prepares for a potential pregnancy every month—hormone levels change, an egg is released from the ovaries, and menstruation occurs if the egg is not fertilized and implanted. This is referred to as the menstrual cycle. It starts on Day 1 of the previous period and ends on the first day of the next period. While the average cycle is 28 days, cycle length can vary greatly. During this monthly cycle, hormones rise and fall.

Not all women with autoimmune disease notice a worsening of their symptoms right before their period or during menses, but quite a few do. Why this happens is not yet fully understood. However, it is thought to be due to the effect that
changing levels of estrogen and progesterone have on immune cell development and activity, and in particular, the sharply falling levels at the end of the cycle and during menses.¹ It may also reflect the relationship between estrogen and pain perception—women tend to report higher levels of pain when estrogen levels are low.²

One study looked at women with SLE and RA to see how pain, fatigue, and disease activity changed over the course of their menstrual cycle. Approximately 35% of women with SLE reported higher levels of pain, fatigue, and disease activity during menses, whereas about 25% of women with RA reported increased pain, fatigue, and disease activity right before and during their period.³ Similar increases in flares have been reported in patients with PsA.⁴

On a bright note, many women with rheumatic disease find that their symptoms are better in the week or so after ovulation at a time when both estrogen and progesterone levels are relatively high.³

References


Changes in Estrogen and Progesterone Levels During the Menstrual Cycle

Adapted from cnx.org/contents/FPtK1zmh@6.27:nMy6SWSQ@5/Anatomy-and-Physiology-of-the-Female-Reproductive-System
Why am I always so tired?

No one knows for certain why patients with rheumatic disease are often overly fatigued, but ongoing inflammation is thought to be a key contributor.

There are several different types of fatigue, including acute, chronic, and peripheral fatigue. When talking about fatigue in women with autoimmune disease, it usually means feeling worn out, exhausted, tired, or lacking energy. This sort of fatigue is not relieved by sleep or rest and can negatively impact physical and cognitive function.\(^1,2\) Not only can this type of fatigue be as disabling as pain, but it also can be hard to manage, with negative impacts on quality of life.\(^1\)

Fatigue is very common in women with autoimmune disease, with more than 50% of women reporting severe fatigue.\(^1\) However, rates of severe fatigue vary across rheumatic diseases.
For instance, more than 80% of women with RA and SLE report significant fatigue—in fact, 53% of women with SLE list fatigue as their most disabling symptom.³

While no one is entirely sure what causes fatigue, the high level of inflammation that accompanies autoimmune disease is the likely culprit. In the setting of inflammation, there is a lot of cross-talk between the immune, nervous, and endocrine systems.²

Normally, pro-inflammatory cytokines released during an infection or inflammation act on the brain, which in turn causes a behavioral response called “sickness behavior.” This response is considered protective, as the drowsiness, decreased activity, and loss of appetite it causes is thought to increase chances of survival.⁴ However, when there are chronically high levels of inflammation in the body, the body goes into overdrive and stress systems become dysregulated, leading to a variety of side effects, including fatigue.¹²

In addition, pain commonly seen in patients with rheumatic disease is known to contribute to restlessness and poor sleep quality, compounding baseline fatigue.³

Finding ways to tackle fatigue can be hard as its triggers remain poorly understood in patients with rheumatic disease. However, it is important to talk about and address fatigue given its widespread nature.
Both conventional disease modifying anti-rheumatic drugs (DMARDs) and, in particular, biologic therapies (e.g., adalimumab, tocilizumab, abatacept) can be effective for the treatment of acute fatigue.\textsuperscript{1,5,6} Controlling disease activity is one of the keys to reducing the severity of fatigue.\textsuperscript{7} It is important to note that patients receiving methotrexate may develop fatigue secondary to use of that medication. Consequently, folic acid supplementation is recommended for all patients receiving methotrexate and may help reduce some side effects, including fatigue. Other strategies to reduce methotrexate-related fatigue include adjusting the drug dose or dosing schedule.\textsuperscript{8}

Patients suffering from chronic fatigue may benefit from behavioral and lifestyle interventions such as cognitive behavioral therapy, self-management interventions, stress management programs (e.g., biofeedback and counseling), graded physical exercise, and efforts to improve sleep hygiene.\textsuperscript{1,3} Furthermore, behavioral and/or pharmacological management of any comorbid mood or sleep disorder can also help reduce fatigue.\textsuperscript{3} With this in mind, it is important for providers to discuss fatigue with their patients to identify ways to address problematic issues and/or identify any underlying conditions that could be contributing to overall fatigue.
References


Which birth control method(s) do you recommend?

Fortunately, there are a lot of great options to consider.

In the general population, an estimated 45% of pregnancies are unintended, suggesting inadequate family planning is a widespread issue. One survey found that nearly half of women with SLE reported having had unprotected sex more than once during the last 3 months, with almost 25% saying this was a regular occurrence. Providers may be partially to blame for this—one survey found that only approximately 50% of rheumatologists reported routinely discussing family planning with their female patients of childbearing age with a systemic inflammatory disease, with another survey finding 33% of women with SLE reported not receiving contraception counseling when starting a new medication.
Thoughtful family planning counseling is an important part of providing comprehensive care to any female of childbearing age. For women with an autoimmune disease, having these discussions takes on even more significance. Not only have many inflammatory rheumatic diseases been associated with increased maternal and fetal complications, but a number of medications used to treat rheumatic diseases can be harmful to developing fetuses.\(^5\)

For the most part, the choice of contraceptive method should reflect individual patient preferences. Factors such as convenience, cost, side effects, reversibility, safety, cultural/religious beliefs, and non-contraceptive benefits should all be considered.

Most common oral and non-oral birth control methods are considered low risk and appropriate to use in patients with inflammatory rheumatic diseases; however, it is important to consider each patient and their specific autoimmune disease when choosing the best option. Currently available birth control methods include intrauterine devices, implants (arm), “depot” injections, progestin-only oral contraceptives, combined hormonal contraceptives (pills, patches or rings), female/male condoms, and diaphragms.\(^5,6\) In terms of birth control pills, lower estrogen-dose formulations have been associated with improved safety profiles compared to pills containing higher doses of estrogen.\(^7\)
There are two caveats to keep in mind regarding birth control in women with rheumatic disease:\textsuperscript{5,6}

1. Long-term progesterone injections have been associated with increased risk of osteoporosis

2. Estrogen-containing contraceptives should be avoided in women with active SLE, SLE with antiphospholipid antibodies, antiphospholipid syndrome, or a history of venous thromboembolism as they may increase the risk of thrombosis and/or exacerbate disease activity

References


How will my disease affect my ability to get pregnant?

While it is somewhat disease dependent, with thoughtful planning, successful pregnancies are realistic for the vast majority of women with rheumatic disease.

Many autoimmune and systemic inflammatory diseases affect women during their childbearing years. The impact of a woman’s disease on her ability to get pregnant is a pressing question for many who have been diagnosed with a rheumatic disease and are considering a pregnancy in the near or even distant future.

There are two issues central to a women’s ability to get pregnant despite her rheumatic disease:

1. Does the disease process itself impact fertility?
2. Do any of the treatment options impair fertility?
The story is a bit mixed, depending on which disease you are looking at.

For women with PsA, the outlook is generally optimistic, with one recent study finding no significant differences in the number of infertility diagnoses, pregnancies, and pregnancy outcomes between women with a diagnosis of PsA compared with women without PsA.\(^1\) Likewise, ankylosing spondylitis is not associated with impaired fertility or an increase in adverse pregnancy outcomes.\(^2\)

For those with RA or SLE, the picture is a bit murkier. There is some evidence that RA impairs fertility, often increasing the time needed to become pregnant and limiting women to fewer children than they may have hoped.\(^3,4\) Fertility problems in women with RA is most often caused by anovulation or unexplained reasons.

But there is some good news for women with RA who are struggling to become pregnant. Several studies have shown that fertility treatments (e.g., in vitro fertilization, ovulation induction) appear to help women with RA become pregnant. It may therefore be wise in women with RA who are having early conception issues to refer them to a fertility specialist.\(^4\)

While overall fertility rates of women with SLE and the general population are similar, women with SLE may also struggle to become pregnant. This can be due to a variety of disease-related causes such as increased rates of primary ovarian failure, menstrual disturbances, and endometriosis.
Increased susceptibility to some infections associated with decreased fertility (e.g., Epstein-Barr syndrome, cytomegalovirus) may also be an issue.\textsuperscript{5} Furthermore, some women with SLE may also have antiphospholipid antibodies, which can contribute to early spontaneous abortion.\textsuperscript{6} Careful pre-conception assessment and planning is very important for women with SLE given that more severe disease (e.g., stage 4 or 5 chronic kidney disease, pulmonary hypertension, heart failure) is associated with serious maternal and fetal risk. That said, women with SLE either in remission or with stable low disease activity can be assured they can have a successful pregnancy with thoughtful management and monitoring by a multidisciplinary care team. Similarly, women with recently-diagnosed early stage or active SLE should be reassured that pregnancy planning can be undertaken once their disease has stabilized at levels of low activity or been in remission for at least 6 months.\textsuperscript{7,8}

It is also known that some drugs commonly used to treat a variety of rheumatic diseases can potentially reduce the likelihood of fertility. As an example, both cyclophosphamide and high-dose nonsteroidal anti-inflammatory drugs (NSAIDs) pose a risk to fertility by causing premature ovarian failure and impaired ovulation and implantation, respectively. Before using these drugs, it is important to discuss their potential risk in women of childbearing age.\textsuperscript{3}
References


How likely is it that I will pass this disease onto my children?

While there certainly is a risk of a woman’s children being diagnosed with the same rheumatic disease as her, it is far from a guarantee.

Given the link between autoimmune disease and genetics, many women worry that their children will inherit their rheumatic disease. This is an important issue, as rheumatic diseases such as RA, PsA, and SLE often occur in family clusters. However, while a positive family history does increase an individual’s risk of developing one of these diseases in the future, it is important to remember that genetics don’t tell the whole story.

Most of the genes involved in the onset of disease like RA, PsA, and SLE are considered susceptibility genes, meaning that, for the disease to actually
develop, there needs to be an environmental trigger to activate the aberrant gene.\textsuperscript{4-6}

For instance, one study found that only about 50\% of the risk for developing RA was determined by genes; the remaining risk was due to non-genetic reasons.\textsuperscript{1} Furthermore, unlike some other medical conditions that follow clear inheritance patterns (e.g., cystic fibrosis), PsA, RA, and most cases of SLE do not follow a predictable or known inheritance pattern.\textsuperscript{4-6}

Thus, it is hard to predict whether any patient’s children will develop the same disease as their parent, even if they inherit one of the susceptibility genes. Recent expert opinion suggests that only 4\% of individuals with a parent or sibling with RA will develop RA themselves.\textsuperscript{7} Risk of an offspring developing PsA appears slightly higher, with data suggesting that approximately 8\% and 16\% of children born to mothers and fathers, respectively, with PsA will go on to develop either psoriasis or PsA.\textsuperscript{8} Similarly, family members of an individual affected by SLE have an estimated 3-10\% chance of developing SLE themselves.\textsuperscript{3} Approximately 1\% of infants born to women with SLE autoantibodies (anti-SSA/Ro-SSB/La) may develop neonatal lupus erythematosus, whose symptoms include skin rash, low blood counts, liver problems, and/or heart block. The skin rash, low blood counts, and liver problems are usually self-limiting and resolve after 3 to 6 months of age, although if heart block is present, it may require a pacemaker at some point in life.\textsuperscript{9,10}
References


Are there any vaccines I’ll need to get before trying to become pregnant?

Possibly, but hopefully most patients with rheumatic disease are already up to date on important vaccinations before trying to conceive.

Ideally, women with rheumatic disease will receive all key vaccinations before starting on an immunosuppressant therapy, such as biologic therapy (including both tumor necrosis factor [TNF] inhibitors and non-TNF inhibitors). After starting a immunosuppressant, women should not receive any live or live attenuated vaccine (e.g., measles/mumps/rubella, varicella, herpes zoster, live attenuated influenza) although killed and recombinant vaccines are OK (e.g., pneumococcal, hepatitis B).
Before becoming pregnant, it is wise to review a woman’s vaccination record and immediately recommend any vaccines that are missing. Unless a woman is on biologic therapy, live vaccines should be given at least 1 month prior to conception to allow for adequate immunity to develop. Once pregnant, live vaccines should be avoided.

It is particularly important to make sure that women are vaccinated against pertussis (whooping cough) as it can be life-threatening to babies. Some of the antibodies the mother produces while pregnant will be passed to the fetus, providing some protection upon birth. It is the same story with seasonal inactivated influenza virus.\textsuperscript{2,6}

The choice of therapy to use during pregnancy to achieve good disease activity should reflect a careful assessment of benefits and risks. Some medications may influence an infant’s immunization schedule; for instance, live vaccines may need to be postponed until after the infant is 5-7 months old.\textsuperscript{3,4,8} In contrast, inactive vaccines (e.g., diphtheria/tetanus/acellular pertussis, hepatitis B) do not need to be held in newborns and should be given in accordance with the CDC immunization schedule.\textsuperscript{5,6} Women should discuss any medications they may have used prior to and during pregnancy with their pediatrician to determine the best timing for live vaccines.

For all breastfeeding mothers with rheumatic disease—even those not on a biologic—both the smallpox (live virus) and yellow fever (live virus) vaccines should be avoided until the newborn is weaned.\textsuperscript{7}
References


What is going to happen to my level of disease activity while I am pregnant?

It may stay the same, it may get better, or it may get worse. A lot depends on the type of rheumatic disease a patient has, but even so, there is no way to tell for certain.

Pregnancy is a time of incredible change for a woman's body. Not only are there physical changes, but several hormone levels undergo major shifts, such as estrogen and progesterone, which steadily increase during pregnancy until rapidly falling after delivery. These changes affect many systems, including the immune system.

Pregnancy triggers a shift in the immune system that promotes fetal survival by decreasing the immune response to the fetus as “foreign.” This shift also impacts disease activity for many women with autoimmune or systemic inflammatory diseases.
Due to very high estrogen and progesterone levels, pregnancy can be a time of relief from symptoms and remission for many women with RA or PsA. For women in remission or with low RA disease activity at the beginning of pregnancy, disease activity tends to remain stable. Women with moderate-to-high RA disease activity at the beginning of pregnancy benefit as well – one study found nearly half of these women experienced symptomatic improvements during pregnancy. In this same study of women with significant baseline disease activity, 17% were in remission during the first trimester and 27% by the third trimester. Women with PsA also seem to benefit during pregnancy, with nearly two-thirds of women in one study reporting improved joint activity while pregnant.

For women with SLE, pregnancy can unfortunately have the opposite effect, with the shift in immune response potentially worsening disease activity. The risk of flares seems to be tied to disease activity during the 6-12 months prior to conception—women with active disease during this period tend to flare during pregnancy, whereas those in remission or with low disease activity have a lower risk of flares.

References


### Changes in female hormones during and immediately following pregnancy

<table>
<thead>
<tr>
<th>Weeks of pregnancy</th>
<th>Estrogen (ng/ml)</th>
<th>Progesterone (ng/ml)</th>
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</thead>
<tbody>
<tr>
<td>Ovulation</td>
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<td>50</td>
</tr>
<tr>
<td>Delivery</td>
<td>30</td>
<td>150</td>
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<tr>
<td></td>
<td>100 times more than when not pregnant</td>
<td>15 times more than when not pregnant</td>
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Adapted from cnx.org/contents/FPtK1zmh@6.27:nMy6WSQ@5/Anatomy-and-Physiology-of-the-Female-Reproductive-System
Which medications are safe/unsafe for me to take during pregnancy?

There are a variety of options available for women with rheumatic disease during pregnancy, although drugs and drug combinations must be approached with care. Unfortunately, some of the medications used to treat rheumatic diseases can be harmful to developing fetuses. Therefore, it is important to discuss treatment options and make sure disease activity is well controlled prior to becoming pregnant.

Until recently, medications were categorized according to their risk on developing fetuses and breastfeeding infants using the FDA pregnancy drug category system of A, B, C, D, X, which ranged from “safe for pregnancy/lactation (A)” to “contraindicated in pregnancy/lactation (X).”
However, some individuals found this type of drug labelling confusing, so since 2015, labels for prescription drugs and biologics in the United States must now include the following information:

- A narrative summary describing the risk of the medication during pregnancy and lactation as well as potential risks to females and males of reproductive age
- Data supporting the summary
- Relevant information to help providers and patients make informed decisions

In patients with rheumatic disease, there are some medications that need to be discontinued prior to conception (e.g., methotrexate, leflunomide), while others may need to be started or adjusted in order to reach or maintain no/low disease activity. Therapy may also need to be adjusted during pregnancy in order to ensure use of safer medications during all trimesters.1,3-5 Discussions regarding the addition or stopping of medications should be discussed both with a patient’s rheumatology provider and her Ob/Gyn.

Managing medications prior to and throughout pregnancy can be complex, and recommendations are not always clear due to the scarcity of data and the number of new medications that have recently become available. Care plans always need to be individualized, with thoughtful consideration of risks and benefits. However, there are medications that can be used before, during, and/or after pregnancy in patients with rheumatic disease to help keep disease activity low and ensure good outcomes for both mom and baby. In 2018, for example, certolizumab pegol became the first anti-
TNF to receive an expanded label change related to pregnancy from the FDA based on studies showing negligible to low transfer of the drug through the placenta and minimal transfer to breast milk from mother to infant.6 The American College of Rheumatology plans to release its first guideline of Reproductive Health in Rheumatologic Diseases in the near future, which should provide additional guidance.

References


Will I be able to breastfeeding my child?

Yes, but just like during pregnancy, careful attention to medication is needed to keep disease activity as low as possible and your baby safe. The good news is that many of the medications deemed safe for use in pregnant women with rheumatic disease can also be safely used during breastfeeding.

As noted in a previous question within this pocket guide, estrogen, progesterone, and prolactin levels all steadily increase during pregnancy. After delivery, however, estrogen and progesterone levels plummet, allowing prolactin, which has been steadily increasing over pregnancy, to stimulate milk production. Furthermore, the immune system shifts back to its “normal” state after delivery.

Thus, depending on the rheumatic disease a woman has been diagnosed with, changing levels of hormones during the immediate post-partum
period may result in a period of relatively quiet disease activity or a period of active disease flares.

During the post-partum period, disease flares are quite common in women with inflammatory arthritis. For instance, nearly 40% of women with RA experience a moderate to severe disease flare within 6 months of delivering their baby. Similarly, studies have found that 40-48% of women with PsA report worsening of joint symptoms or high disease activity in the first year after giving birth. The percentages are even higher for women with ankylosing spondylitis, with 90% of women reporting increased disease activity during the postpartum period.

In contrast, data is mixed for women with SLE, with some studies reporting increased flares during the postpartum period while others have reported no increase in disease activity.

Women who breastfeed have higher prolactin levels compared with women who choose not to nurse, although levels gradually decrease over time. Interestingly, some studies have found that higher prolactin levels may be associated with increased disease activity for patients with RA and SLE—indeed, one small study found that breastfeeding itself was associated with increased disease activity in women with rheumatoid and inflammatory arthritis.

Women with rheumatic disease who wish to breastfeed should be encouraged to do so as there are nursing-safe options available. Recommendations regarding those medications that can be considered safe for use during breastfeeding tend to mirror medication recommendations during pregnancy.
Table. Summary of Medications and Compatibility with Breastfeeding

<table>
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<td>Cyclosporine</td>
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<tr>
<td>Heparin</td>
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IVIG = intravenous immunoglobulin; NSAIDs = nonsteroidal anti-inflammatory drugs
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<th>Preferred medications (low-to-moderate risk)</th>
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<td>Canakinumab</td>
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</table>
References


What is going to happen to my disease as I reach menopause?

It is hard to know, as every woman is different, but in part, it depends on which type of rheumatic disease you have been diagnosed with as well as individual factors.

As women age, levels of both estrogen and progesterone steadily drop, with increased rates of decline seen during the perimenopausal, menopausal, and post-menopausal years.\(^1\) While other sex hormones are likely involved, decreasing estrogen levels affect the immune system in a number of ways.\(^2\) Aging itself also affects how the immune system works. This, combined with changing hormones, can affect activity levels of immune-mediated rheumatologic diseases.\(^3\)

For women with SLE, the news is generally positive. For them, menopause is typically associated with reduced disease activity and
decreased frequency of flares. Unfortunately, the news is somewhat mixed for women with other inflammatory, immune-mediated conditions. For instance, some women with RA may experience increased disease activity, worse functional status, and accelerated rate of functional decline during or after menopause. However, it is important to remember that every patient is different. For instance, in post-menopausal women, longer exposures to estrogen (e.g., history of pregnancy, hormone replacement therapy, and/or longer length of reproductive years) are associated with less severe functional decline.

In contrast, it isn’t clear if PsA disease activity changes after menopause. Women often experience PsA flares during other low estrogen states (e.g., postpartum), and women with psoriasis often notice that their disease worsens with menopause. As such, some women may notice an increase in disease flares.

While gout can be caused by a number of factors, the overall risk of incident disease dramatically increases post-menopause, with one study finding menopause increased the risk of incident gout by 26%. In this case, the increased risk reflected the loss of protective effects from estrogen and progesterone in keeping serum uric acid within normal ranges through the promotion of efficient urate clearance in the kidneys.

Women with inflammatory rheumatic disease are already at increased risk for common comorbidities compared with the general population, including cardiovascular disease, osteoporosis,
and type 2 diabetes. The increased risk is further compounded with the onset of menopause. Thus, ongoing assessment and management of these comorbidities in patients prior to and during menopause, as well as in the post-menopausal period, should be part of a patient’s overall plan of care.\textsuperscript{9-12}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{hormonal-shifts.png}
\caption{Hormonal Shifts Seen During Menopausal Transition}
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Adapted from my.clevelandclinic.org/health/diseases/15224-menopause-perimenopause-and-postmenopause
References


