Contraceptive Options for the Patient with Pulmonary Arterial Hypertension

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The World Health Organization describes contraception as desirable for many reasons. It allows families to make informed choices about their reproductive years. It allows family planning, with spacing of children, leading to better bonding between mother and child, higher exclusive breastfeeding rates, and improved health of the mother for a future pregnancy.[1]

Unintended pregnancies continue to occur at an astronomically high rate in the US, as high as 35% by most recent data,[2] and of course, since women with pulmonary arterial hypertension (PAH) are not exempt from this statistic, it is imperative that as care providers, we help our patients to plan ahead. In their case, maternal health is our main concern.

Weiss and colleagues, reporting on pregnancy outcomes with PAH between 1978 and 1996, found a maternal mortality of 36% in Eisenmenger syndrome, 30% in idiopathic PAH, and 56% in secondary PAH.[3] A more recent systematic review reported slightly more optimistic pregnancy outcomes from 1997 to 2007. Still, maternal mortality ranged from 17% to 33%, depending on the exact etiology of pulmonary hypertension.[4] It is therefore very clear that in the setting of PAH, contraception is important and potentially lifesaving.

PULMONARY HYPERTENSION IN PREGNANCY

PAH can be idiopathic or related to other medical problems. Regardless of its cause, significant pulmonary hypertension creates problems during pregnancy. Many of the risk factors for PAH including HIV, collagen vascular disease, and congenital heart disease are not uncommon during the reproductive years, so as medical practitioners, we can expect to see any number of patients with PAH at risk for pregnancy.[5]

The hemodynamic changes seen in pregnancy are substantial. In a normal pregnancy, there is a 50% increase in blood volume, a similar increase in cardiac output, as well as increases in heart rate and stroke volume. Systemic vascular resistance and blood pressure both decrease during gestation.[6] During the delivery, sudden changes in venous return and right ventricular filling may occur related to expected blood losses, decreased venous return related to systemic vasodilation from epidural anesthesia or from pooling of blood in the lower extremities from vena caval compression by the gravid uterus.[7] This can worsen right ventricular preload and lower cardiac output, leading to sudden deterioration, and in many cases, can lead to maternal death. At the same time, volume excess on top of an already enlarged right ventricle can cause left ventricular compression via ventricular interdependence, also reducing cardiac output.

Those women who choose to proceed with pregnancy in the setting of PAH can expect to be severely limited in their activities. They should anticipate early hospitalization, perhaps as early as fetal viability, for maternal and fetal surveillance. They will need supportive therapy with supplemental oxygen and vasodilating drugs. To prevent thromboembolic events, they may need anticoagulation, and volume status must be watched carefully.[5,7] Management should be carefully coordinated with the pulmonary hypertension team, who may consider inhaled nitric oxide therapy periprocedurally as treatment to reduce pulmonary vascular resistance while sparing the systemic vascular resistance. Additionally, adjustments to long-term pulmonary hypertension therapy will generally be required.

Perhaps a patient might be willing to tolerate all these risks for the sake of motherhood, but the fetus is not exempt from morbidity and mortality. Data suggest that there is an increased risk of prematurity and fetal growth restriction, and a risk of stillbirth or neonatal death that ranges from 7% to 13%.[4] In addition, medications typically used in PAH carry significant fetal risks as well. Warfarin, a widely used oral anticoagulant, is a known human teratogen, with varying effects on the fetus, depending on the period of exposure to the drug. Exposure during organogenesis, particularly the sixth through ninth weeks, puts the fetus at risk for warfarin embryopathy. Warfarin embryopathy involves typical facial features of nasal and midface hypoplasia, and stippled vertebral and femoral epiphyses. Exposure during the first trimester can also lead to increased risk of miscarriage: in those patients taking over 5 mg of warfarin daily, the incidence of spontaneous abortion can be as high as 72%.[8] Second- and third-trimester exposures can result in hemorrhage, leading to deformation of several fetal organs. Congenital malformations associated with second- and third-trimester exposure to warfarin include agenesis of the corpus callosum, Dandy-Walker malformation, midline cerebellar atrophy, microcephaly, ophthalmic atrophy, and blindness. Developmental delay and mental retardation have also been described.[9]

Among the three major classes of drugs used for the treatment of PAH, endothelin receptor antagonists such as bosentan (trade name Tracleer) have also shown teratogenic effects in animal studies and must be avoided. Though there are no studies in human pregnancy, studies in

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rats and rabbits have shown that bosentan can lead to malformations of the fetal head, mouth, face, and large blood vessels. Extra precautions are necessary when using bosentan since it can interfere with metabolism of contraceptives, making them less effective. The prescribing information for this drug recommends a highly effective method of contraception or two methods of less effective birth control when taking bosentan.[10] Similar methods are also recommended with ambrisentan, another endothelin receptor antagonist, though it has not been shown to decrease the effectiveness of combination contraceptives.[11]

Although pregnancy is never recommended in PAH, some women do become pregnant—either because they were newly diagnosed with pulmonary hypertension *during* the pregnancy, because of contraceptive failures, or occasionally intentionally, despite the advice of their physicians. For these patients, the two other classes of PAH medications can be considered for use during pregnancy. Phosphodiesterase inhibitors like sildenafil (trade name Revatio) have been assigned to pregnancy category B by the FDA. Animal data have not shown increased risk of teratogenicity even at doses correlating with 40 times the maximum recommended human dose.[12] However, there are no controlled data in human pregnancy and no long-term observational studies to assure its safety. Similarly, prostacyclins like epoprostenol (trade names Flolan and Veletri) have been assigned to pregnancy category B by the FDA. Most experts suggest that the benefits of using this drug in pregnancy outweigh the potential embryo-fetal risks. Animal studies have failed to reveal evidence of fetotoxicity or impaired fertility at doses from 2.5 to 4.8 times the recommended human dose.[13] As in the case of the phosphodiesterase inhibitors, there are no controlled data in human pregnancy.

The following review will describe a number of contraceptive options available to a patient with PAH, their effectiveness, and potential side effects. The long-term benefits to maternal health should be quite obvious, given that pregnancy itself could be the biggest contributor to shortening a patient's life expectancy.

CONTRACEPTIVE OPTIONS

Reversible Contraception

Estrogen and progestin combinations. Estrogen and progestin pills have been available in the United States since 1960. Dosage and formulations have changed over the years, making them safer and more tolerable, and side effects have diminished. More recently, various alternative delivery systems have come on the market, including transdermal patch, and transvaginal ring.

Combination oral contraceptive pills consist of an estrogen and a progestin. They are safe and effective, and well tolerated by most women, but do need to be taken on a daily basis. Their effectiveness decreases substantially with inappropriate use, as evidenced by the higher failure rate with typical use vs perfect use, 8% vs 0.3% respectively.[14] The estrogen-progestin combination is taken daily for 3 weeks; during the fourth week, a placebo is administered, leading to withdrawal bleeding. Some prescription formulations are also available for those patients who want to minimize withdrawal bleeding, with extended administration of estrogen and progestin, providing the placebo approximately every 3 months.

The main mechanism of action of estrogen-progestin combination contraceptives is prevention of ovulation by suppression of the hypothalamic-pituitary axis. Estrogen specifically suppresses follicle stimulating hormone (FSH) release; and progestins suppress luteinizing hormone (LH). Progestins also thicken cervical mucus, making sperm passage into the uterus more difficult. Both estrogen and progesterone have local effects on the endometrial milieu, rendering it unfavorable for implantation.[14]

Patients taking estrogen-progestin combinations can expect a fairly predictable cycle, less bleeding than when not using contraception, and less pain associated with menses. Other benefits include increased bone density and decreased risk of endometrial and ovarian cancer. In some studies, they have also been shown to be useful in treatment of mild acne and premenstrual syndrome. The most common side effects of estrogen-progestin combinations are headache, dizziness, breast tenderness, breakthrough bleeding, and decreased libido. Most of these tend to resolve over time, or can be minimized by choosing the lowest dose pill that would be effective for each patient.

The transvaginal ring (trade name NuvaRing), with etonogestrel and ethinyl estradiol, has the same mechanism of action as combination birth control pills. The hormones are released from the core of the ring at a steady rate and ovulation is prevented. A new ring has to be placed within 5 days of the first day of the woman's menstrual cycle. After 3 weeks, the ring is removed, and the patient will then have her normal cycle. The method is considered highly effective, with a failure rate equivalent to that of combination pills.[15]

The contraceptive patch (trade name Ortho Evra) provides transdermal administration of norelgestromin and ethinyl estradiol.[16] A new patch is applied to the skin every week for 3 weeks; a patch-free week follows, to allow withdrawal bleeding. The novel delivery system may be appealing to those patients who prefer weekly application of the patch, rather than daily dosing of the birth control pill. Although still an effective method, with 1.2 pregnancies per 100 woman years, with typical use, the failure rate can be as high as 8%. This may be related to the known increased risk of failure in women who weigh over 90 kg, in addition to variations in transdermal absorption from patient to patient.[14]

Progestin-only contraception. Progestins, like estrogen and progesterone in combination, prevent pregnancy by thickening cervical mucus, and thinning out the endometrial lining, turning it into an inhospitable environment to the fertilized egg wishing to implant. The effect on suppression of ovulation will vary depending on the dose of progestin. For example, the mini pill will only suppress ovulation about 50% of the time, whereas moderate and high-dose progesterone delivery systems will prevent anywhere from 97% to 100% of all ovulations.[14]

With many progestin-only methods, unfortunately, a common side effect will be irregular periods. Some other common side effects include mood swings, weight gain, headache, acne, and depression.

The progestin-only pill (trade name Micronor), is commonly known as the "mini pill." It contains norethindrone, a progestin found in many combination birth control pills, but in this scenario, it acts alone to prevent ovulation. The mini pill may be prescribed to those patients who are post partum, who are using lactational amenorrhea as a method of contraception. In combination with breastfeeding, the norethindrone pill is virtually 100% effective at preventing pregnancy and does not impair breast milk production.[14] Norethindrone by itself does not consistently prevent ovulation, so it relies mostly on its effect on the cervical mucus and on the endometrium for prevention of pregnancy. One disadvantage is that it has to be taken daily, and at the same time every day. For the nonlactating patient, the progestin-only pill has a higher pregnancy rate than combination pills, and would not be considered reliable contraception for the patient with PAH.

As an injectable progestin, *depot medroxyprogesterone acetate* (*trade name Depo-Provera*) has been in use in the United States since 1992. The dose of 150 mg is given intramuscularly every 90 days. The mechanism of action is the same as for other progestins. Among its many advantages is the long duration of action, with a contraceptive effectiveness that is comparable to combination birth control pills. Among its disadvantages, irregular bleeding is the most common side effect. In addition, loss of bone mineral density has been reported. Reassuringly, this bone loss is reversible once the drug has been stopped.[14] Depot medroxyprogesterone could be useful in those patients with PAH who need effective contraception while transitioning to one of the more longer-acting and effective methods.

The subdermal implant with etonogestrel (*trade name Implanon*) (Figure 1) is a very reliable method of long-acting contraception; it is more than 99% effective.[17] It is approved for use for up to 3 years. Like other progestin-only methods, its mechanism of action is to suppress ovulation, thicken the cervical mucus, and render the atrophic endometrium averse to implantation. Return to fertility upon removal is relatively quick, so a second implant should be inserted at the time of the first's removal to prevent an unintended pregnancy. If another implant is not placed, another highly effective method of contraception should be chosen. Though the implant has an irregular bleeding profile that may be bothersome to some patients, this common side effect should not prevent them from choosing this excellent method of contraception.

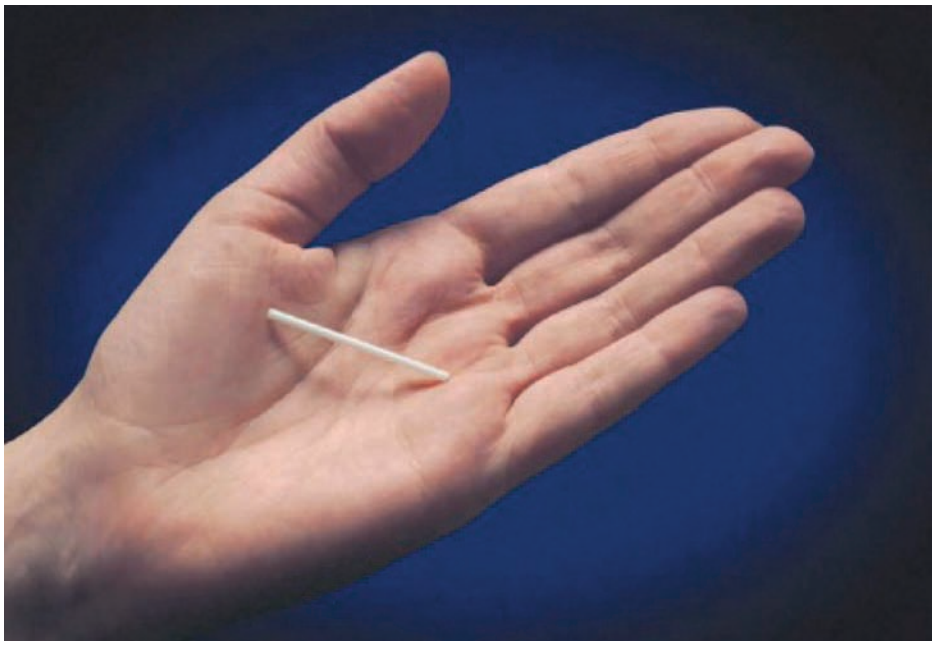

Figure 1: The Implanon system rod. From *Williams Gynecology*, 2008, with permission.

A levonorgestrel-containing intrauterine device (*IUD*), shown in Figure 2, is available (*trade name Mirena*) in the United States and is approved for up to 5 years of use.[18] The typical failure rate of this device is 0.1%. Since it releases the progestin locally into the uterus, there are fewer systemic side effects, although they are still possible. The levonorgestrel thickens cervical mucus, thins the endometrium, and may make sperm less mobile. Like the copper IUD that we will discuss later, this device is an excellent choice for patients with PAH, given that it is long acting and highly effective.

Thromboembolic Risk Controversy

Before moving on to a review of nonhormonal contraceptive options, an important question is worth discussing: is the fear of hormonal contraception warranted in PAH patients who are anticoagulated?

Quite clearly, the risks of progesterone-only contraceptives have not been substantiated in the literature, and remain a safe option for patients with PAH, whether anticoagulated or not. But what is it about estrogen-containing contraception that gives us pause? Estrogen increases hepatic production of factor VII, factor X, and fibrinogen, thus increasing the risk of venous thromboembolic events (VTE) in users of combination estrogen-progestin contraceptives.[19] A case-control study done in the US, involving 196 cases of VTE and 746 age-matched controls, showed an odds ratio (OR) of 4.07 for venous thromboembolism associated with current combination oral contraceptive use.[20] In absolute terms, however, the risk of VTE during pregnancy is higher than the risk associated with combination contraceptive use. Indeed, the risk of death is higher in pregnancy, across all age ranges, than with use of any contraceptive method, whether estrogen-containing or not, as shown in Table 1. For the pulmo-

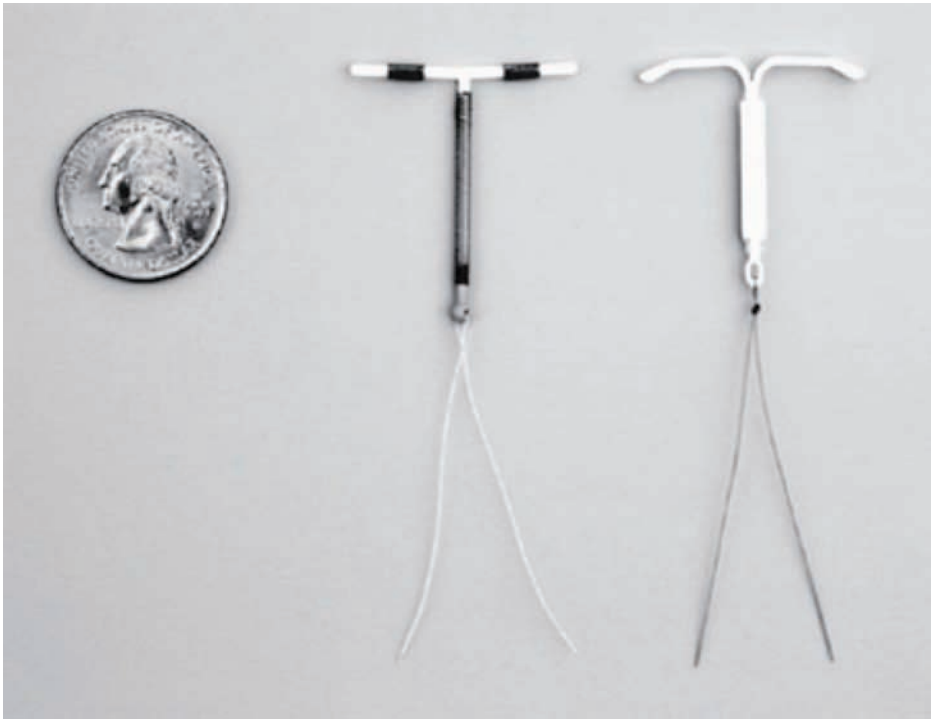

Figure 2: The copper-containing Paragard T 380A (left) and the levonorgestrel-releasing Mirena (right). From Williams Gynecology, 2008, with permission.

nary hypertension patient specifically, consensus guidelines recommend use only if a patient is receiving concomitant anticoagulation. An added issue for some PAH patients is that warfarin can also lead to menorrhagia. Thus, in well-anticoagulated women, the use of combination oral contraceptives could be useful, particularly to reduce menstrual blood loss, without increasing the risk of VTE.[21]

Nonhormonal contraception. *The copper-T IUD* (*trade name Paragard*) shown in Figure 2 is approved for use for up to 10 years.[22] Other than permanent sterilization, it is the longest-acting contraceptive available today. Though the precise mechanism of action of IUDs in general has not been clearly defined, they are thought to prevent fertilization. The copper ions released by the IUD trigger an intense local inflammatory reaction, leading to lysosomal activation and other inflammatory events that are spermicidal.[14] In addition, the endometrium is rendered unsuitable for implantation precisely because of the same inflammatory reactions. Menstrual cycles can be very predictable with the copper-T, and with a failure rate of 0.8%, it is a great contraceptive choice for patients with PAH.

Table 1: Birth-Related or Method-Related Deaths Per 100,000 Fertile Women by Age Group

Method	15-24 Years	25-34 Years	35-44 Years
Pregnancy	5.1	5.5	13.4
Abortion	2.0	1.8	13.4
Intrauterine device	0.2	0.2	0.4
Rhythm, withdrawal	1.3	1.0	1.3
Barrier method	1.0	1.3	2.0
Spermicides	1.8	1.7	2.1
Oral contraceptives	1.1	1.5	1.4
Implants/injectables	0.4	0.6	0.5
Tubal sterilization	1.2	1.1	1.2
Vasectomy	0.1	0.1	0.1

From Williams Gynecology, 2008, with permission.

Barrier methods include male and female condoms, diaphragm, and cervical cap, preferably used in combination with spermicides and microbicides.[14] They act as a physical and chemical barrier so that sperm cannot get to the ovum. Spermicides on their own are not considered effective contraception. Mechanical barrier methods, if used at all, should be used in combination with a spermicide. With failure rates as high 36% with typical use, they should not be considered reliable for patients with PAH.[14]

Natural family planning methods include the calendar rhythm method, the symptothermal method, and the cervical mucus rhythm method, among several others. These methods tend to be cumbersome, and rely on a patient's cycle being very predictable. They all include some degree of abstinence that varies depending on where the patient is on her menstrual cycle. The patient attempts to time intercourse to avoid her fertile days, whether by detecting slight basal temperature changes that occur post ovulation, evaluating the consistency of cervical mucus, or by using home testing kits to detect the preovulatory LH rise. Quite clearly, these methods do not provide the effectiveness that other methods provide. Their failure rate can range anywhere from 2%-3% with perfect use to 20% with typical use.[14] They are mentioned in this review for completeness, and not to endorse them in any way in the contraceptive management of a patient with PAH.

Permanent Contraception

Female sterilization. These procedures can be performed post partum, post abortion, or electively if nonpuerperal. The surgical approach can vary depending on timing. For example, a patient immediately post partum may undergo sterilization via a periumbilical incision, while a patient who just underwent termination of pregnancy, and whose uterus would be substantially smaller than someone who had just delivered a term infant, would

require a supraumbilical incision. Once in the abdominal cavity, most sterilization procedures are essentially the same. They involve ligation and resection of a segment of Fallopian tube, which is sent to the pathologist for tissue confirmation.

Procedures done electively can also be done by a laparoscopic approach: these involve both ligation and resection of a segment of the Fallopian tubes, or interruption of the tubes via a variety of permanent surgical clips or rings. All of these methods have favorable long-term success rates.

For all these procedures, there is the inherent risk of surgery—infection, increased blood loss, damage to other internal organs—and in the case of laparoscopic procedures, the greater risk of death due to complications of general anesthesia.[6]

More recently, hysteroscopic sterilization procedures have become *en vogue*. These are done going through a natural orifice, the patient's cervix, to go into the endometrial cavity, visualize the tubal ostia, and obliterate them in a variety of ways. Two examples of these hysteroscopic procedures are the Adiana® and Essure® systems.[23,24] The first uses a medical-grade silicone insert and radiofrequency to block the tubes, while the latter (Figure 3) uses a titanium insert. Both of these procedures are usually done in a physician's office, under local anesthesia, and sometimes with conscious sedation. For a patient with PAH, the safest place to perform any procedure would be the operating room, but a procedure that limits surgical time and the need for regional or general anesthesia would certainly be desirable.

Male sterilization. Safe and effective, vasectomy is performed under local anesthesia. A small incision is made in the scrotum, and a segment of vas deferens is removed bilaterally, to prevent the passage of sperm from the testes. A procedure that averages about 20 minutes to perform in the outpatient setting, vasectomy is cheaper than female sterilization, has fewer complications, and a 10- to 37-fold lower failure rate.[25] It is important to realize, however, that vasectomy is not immediately effective since the sperm that were beyond the resected segment of vas deferens will take approximately 3 months to be expelled. Since the procedure-related mortality rate is 12 times higher with female sterilization, vasectomy remains the safest, most efficacious, and least expensive method of sterilization. For any couple and especially for the partners of our patients with PAH, physicians should recommend vasectomy when providing counseling on sterilization, despite the popularity of bilateral tubal ligation procedures.

Figure 3: The titanium insert of the Essure procedure. Courtesy of Conceptus, Inc, Mountain View, CA.

It is clear that in terms of effectiveness and permanence, sterilization is the best method to prevent pregnancy for the patient with pulmonary hypertension. For those patients who are not good surgical candidates, it is important to remark on the effectiveness and high desirability of long-acting reversible contraception (LARC) as the most reliable nonpermanent option for patients with PAH. As shown in Figure 4, those methods that fall under this category would be contracep-

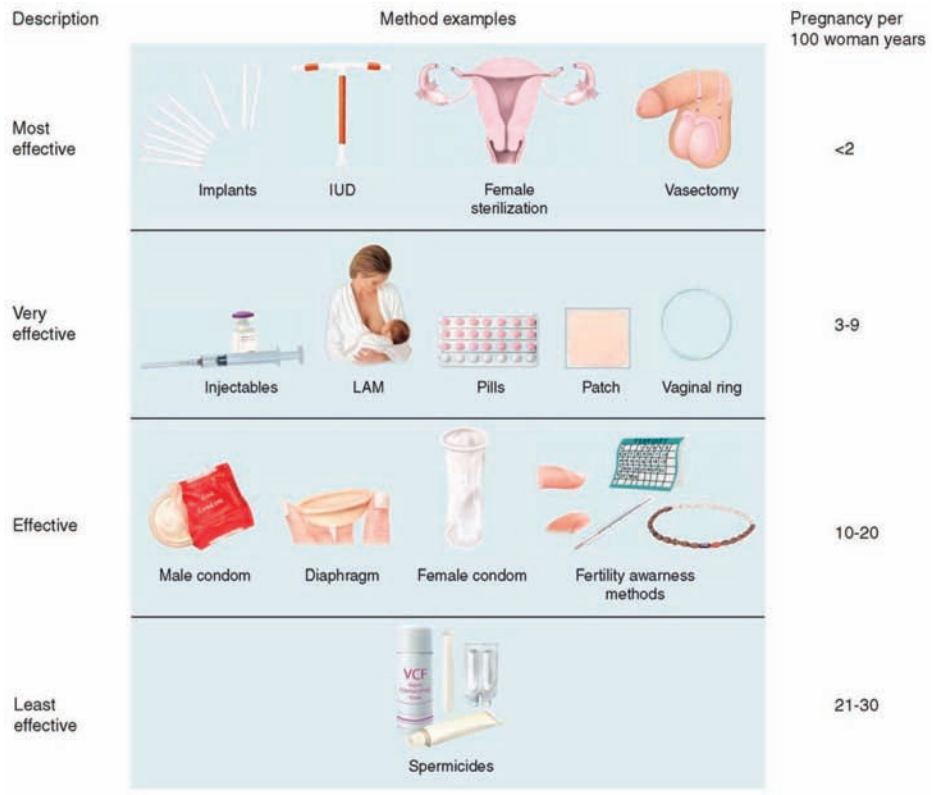

Figure 4: Birth control methods, displayed according to effectiveness in preventing pregnancy. From *Williams Gynecology*, 2nd edition, with permission.

tive implants, such as the etonogestrel single-rod implant, and either of the IUDs. Their effectiveness approaches that of sterilization. These first-choice reversible methods require "a single act of motivation for long-term use," eliminating adherence and user dependence from the effectiveness equation.[26] They should be discussed with our patients as being among the best contraceptive options available.

CONCLUSION

For most women, especially those with PAH, contraception poses far less risk than pregnancy. Even with the real increased risk of thromboembolic events in those using estrogen-containing contraception, albeit counteracted by chronic anticoagulation, pregnancy with PAH carries such a high risk of mortality that any efforts to prevent it are warranted. Safe and effective LARC methods are available, and if feasible based on lower surgical risk, permanent sterilization should be advised in these patients.

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