Cutaneous Lymphoma: Effect of Treatment on Reproductive Health and Implications for Patient Education

There are limited data available on which to base recommendations for patients with cutaneous lymphoma regarding fertility preservation, contraception, pregnancy, and lactation. Below is a summary of data that are available (much of it from animal studies) as well as recommendations to be individualized based on clinician judgment and patient factors.

Agent	**Fertility Effects** Effect on spermatogenesis (sperm production) and ovarian reserve *Implications regarding fertility preservation*	**Safety of Conception** Mutagenicity *Implications regarding contraception*	**Usage in Pregnancy** Teratogenicity and risk of fetal harm *Implications regarding safety of pregnancy*	**Safety of Lactation** Excretion in breast milk *Implications regarding breast feeding*
Topical Agents				
Topical Steroids	<u>Male</u> • Long term oral steroid use has been linked to decreased levels of testosterone and therefore may be associated with temporarily decreased sperm production [1] • No data is available for topical steroids. *No need to sperm bank* <u>Female</u> • Long term steroid use by mouth has been associated with irregular menses and could temporarily affect fertility. [2] • No data is available for topical steroids. *No need to freeze eggs or embryos*	<u>Male and Female</u> • Corticosteroids are not known to have mutagenic effects. This has been tested in three separate laboratory assays [3] *No need for contraception during treatment*	• Pregnancy Class C • Some studies have shown an association of oral steroid use in early pregnancy with birth defects such as orofacial cleft; however many other studies do not indicate this.[4-12] • There is a small association of low birth weight with use of high potency topical steroids. [10-12] *No need to avoid pregnancy while on treatment if risks of therapy outweigh the benefits*	• Corticosteroids are excreted into breast milk. However, at low doses of corticosteroids, the amount of drug in breast milk is unlikely to affect the baby. .[13-16] *No need to limit breast feeding while on this therapy if mothers are taking less than the equivalent of 20mg of oral prednisone [16]* *Consider avoiding topical steroid use on skin that will be in direct contact with your baby shortly before breastfeeding.*

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Topical Agents				
Topical Retinoids **Bexarotene, topical** (Targretin®) – Retinoid **Tazarotene, topical** (Tazorac ®) —Retinoid	Male • Bexarotene reduces testicular function in animal studies. [17] • There are no long term studies of in animals. [17] *No need to sperm bank.* Female • There are no long term studies of fertility or carcinogenic potential in animals. [17] *No need to freeze eggs or embryos unless patient desires*	Male and Female Bexarotene has not been known to cause mutations in sperm or eggs, although formal studies have not been done. Male • Effective contraception (condoms) should be used during sexual intercourse & for at least one month after the last drug dose. [17] Female • Effective contraception must be used for one month prior to initiation of therapy, during therapy & for at least one month following discontinuation of therapy. [17] *Contraception throughout treatment and for at least one month after treatment*	• Pregnancy category X [17] • Bexarotene and similar drugs caused birth defects and pregnancy loss in animal studies. [17] [18] • Topical bexarotene is absorbed through the body and should be treated the same as bexarotene by mouth. [19] • May cause fetal harm when administered to a pregnant woman. [17] *Avoid if pregnant or intending to become pregnant* [17]	• It is unknown whether bexarotene is excreted in breast milk.[17] *A nursing mother should not use bexarotene* [17, 18]

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Topical Agents				
Mechlorethamine, topical (Valchlor ®) —Alkylating agent	<u>Males</u> • Intravenous (IV) mechlorethamine can impair fertility and cause low sperm counts. [21, 22] • Studies of mechlorethamine applied to the skin do not show absorption into the body. Therefore, topical use is very unlikely to impact fertility but this has not been formally studied. *No need to sperm bank unless patient desires* <u>Females</u> • IV mechlorethamine has been associated with temporary or permanent loss of menstruation and fertility. [21, 22, 24] • Studies of mechlorethamine applied to the skin do not show absorption into the body. Therefore, topical use is very unlikely to impact fertility but this has not been formally studied. *No need to freeze eggs or embryos unless patient desires*	<u>Males and Females</u> • Topical mechlorethamine has not been known to cause mutations in sperm or eggs, although formal studies have not been done. *Contraception throughout treatment.*	• Pregnancy Category D [23] • Intravenous mechlorethamine causes birth defects in animal models. [23] • There are reports of women who have been treated with IV chemotherapy regimens including mechlorethamine, who subsequently had normal pregnancies and normally developed offspring[24] *Pregnancy should be avoided during treatment*	• Not known whether mechlorethamine is excreted in human milk. *Drug is not recommended in nursing women [23]*

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Topical Agents				
Topical Imiquimod, topical (Aldara® or Zyclara®)—Immunomodulatory Agent	Males and Females • Studies in rats with oral and topical imiquimod did not show an impact on growth, fertility, or reproduction. No studies have been done in humans. [25] *No need to sperm bank or freeze eggs or embryos.*	Males and Females • Topical imiquimod has not been known to cause mutations in sperm or eggs, although these studies have not been done. *No need for contraception during treatment*	• Pregnancy category C • Birth defects were seen in offspring of female rats taking imiquimod by mouth. [25] • There are 12 case reports of pregnant women who used topical imiquimod and subsequently had normal pregnancies and normally developed offspring. [26-28] *Avoid pregnancy while on treatment unless risks of stopping therapy outweigh the benefits [28]*	• It is not known whether imiquimod is excreted in breast milk and the effect on infants is not known. However, topical imiquimod is absorbed throughout the body. [25] *Drug is not recommended in nursing women*

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Systemic Treatment, Non-Chemotherapy				
Bexarotene (Targretin®) – Retinoid	• Long-term studies in animals to assess risk of causing cancer or impact on fertility have not been conducted[29] <u>Male</u> • Bexarotene reduced testicular function in animal studies. [17] *No need to sperm bank unless patient desires to father a child in the near future and interruption of treatment would not be possible.* <u>Female</u> • No data available *Offer egg or embryo freezing if patient desires*	• Bexarotene has not been known to cause mutations in sperm or eggs. <u>Male</u> *Effective contraception (condoms) must be used during sexual intercourse & for at least one month after the last drug dose. [29]* <u>Female</u> *Effective contraception must be used for one month prior to initiation of therapy, during therapy & for at least one month following discontinuation of therapy. [29]*	• Pregnancy category X [29] • Causes birth defects in rats. • Developmental abnormalities included cleft palate, problems with bone formation, and abnormally small ears and eyes. At higher doses, it caused pregnancy loss. [29] • Like other retinoids, considered teratogenic & embryotoxic in oral-dose studies. [30] *Avoid if pregnant or intending to become pregnant [29]*	• Unknown whether bexarotene is excreted in breast milk [29] *Drug is contraindicated in nursing women [30]*

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Systemic Treatment, Non-Chemotherapy				
Interferon- alpha (IFN-α)	<u>Male</u> • No significant adverse effects seen in male fertility (IFN α 2a). [31, 32] *No need to sperm bank unless patient desires* <u>Female</u> • In a study of monkeys there were temporary effects on menstrual cycles that returned to normal menstrual cycles after stopping the medication. [31] *No need to freeze eggs or embryos unless patient desires*	• No evidence of causing mutations in sperm or eggs (IFN α 2a). [31] • Conflicting data available on the detection of gene abnormalities after treatment with (IFN α 2a). [31] *Contraception throughout treatment and for one year after treatment [31]*	• Category C drug • Does not cause birth defects in animal studies • No adequate & well-controlled studies conducted in pregnant women. [31] • Several cases of use during pregnancy suggest there may be a risk of premature delivery but the infants were normal. [32-34] *Avoid use during pregnancy unless the benefit to the woman justifies the risk to the baby.*	• Unknown whether it is excreted in breast milk (IFN α 2a). [31] *The drug should not be used by nursing women. [32]*
Romidepsin (Istodax®) – HDAC inhibitor	<u>Male</u> • Animal studies show some impact on testicles during treatment. There are no studies on long-term effects after discontinuing treatment. [36] *Offer sperm banking if patient desires* <u>Female</u> • Animal studies show some impact on ovaries. There are no studies on long term effects after discontinuing treatment.[36] *Offer egg or embryo freezing if patient desires*	• No data available on ability to cause mutations in sperm or eggs. • Estrogen-containing contraceptives may be less effective when used with romidepsin. Caution is advised. [36] *Contraception throughout treatment and for one year after treatment*	• Category D drug • No adequate & well-controlled studies conducted in pregnant women • In animals, the drug led to birth defects and pregnancy loss. [36] *Avoid if pregnant or intending to become pregnant in the near future.*	• Excretion in milk is unknown. [36] *Due to the potential for serious adverse reactions in nursing infants, breast feeding should be avoided. [36]*

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Systemic Treatment, Non-Chemotherapy				
Vorinostat (Zolinza®) – HDAC inhibitor	<u>Male</u> • In male animal studies there was no effect fertility. [37, 38] *No need to sperm bank unless patient desires* <u>Female</u> • No data available *Offer egg or embryo freezing if patient desires*	<u>Male</u> • No data available <u>Female</u> • In animals, the drug caused genetic changes in the ovaries. [37] *Contraception throughout treatment and for one year after treatment*	• Category D drug • Can cause fetal harm when administered to a pregnant woman. [37, 38] *Avoid if pregnant or intending to become pregnant in the near future.*	• Excretion in milk is unknown. [37] *Due to the potential for serious adverse reactions in nursing infants, breast feeding should be avoided.[37]*

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Systemic Chemotherapy and Radiation Therapy				
Exposure to chemotherapeutic agents or radiation can cause mutations in sperm or eggs and birth defects in a developing fetus. [39] It is important to avoid getting pregnant or fathering a baby during treatment, and for a period after treatment. The amount of time to wait will vary based on individual patient and treatment factors. To allow for potentially damaged sperm or eggs to be cleared or repaired before attempting to have a baby, at least six to 12 months wait after treatment is recommended. [40, 41] In addition, women may be advised not to become pregnant during the time at which they are at highest risk for relapse or recurrence. [41]				
Methotrexate – (antimetabolite)	<u>Male</u> • Injury to sperm, transient low sperm counts, and infertility may occur [42] • This medication typically causes only temporary damage to sperm production [43] *No need to sperm bank unless patient desires to father a child in the near future and interruption of treatment would not be possible.* <u>Female</u> • Defective egg production, menstrual dysfunction, and infertility have been reported [42] [43] *No need to freeze eggs or embryos unless patient desires*	<u>Male and Female</u> • Causes chromosome damage. Men and women should avoid conception during and immediately following treatment so that normal production of sperm or eggs can be established. [42] *Contraception throughout treatment and for at least 12 weeks after treatment[42]* *OR for one year after treatment*	• Pregnancy category X [44] • Abortion, fetal death, and/or birth defects have occurred. [42] *Pregnancy should be avoided during treatment*	• Distributed into breast milk [42] *Should not be used by nursing women [42]*

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Systemic Chemotherapy and Radiation Therapy				
Exposure to chemotherapeutic agents or radiation can cause mutations in sperm or eggs and birth defects in a developing fetus. [39] It is important to avoid getting pregnant or fathering a baby during treatment, and for a period after treatment. The amount of time to wait will vary based on individual patient and treatment factors. To allow for potentially damaged sperm or eggs to be cleared or repaired before attempting to have a baby, at least six to 12 months wait after treatment is recommended. [40, 41] In addition, women may be advised not to become pregnant during the time at which they are at highest risk for relapse or recurrence. [41]				
Liposomal Doxorubicin (Doxil®) – anthracycline	<u>Male</u> • No human data but injury to testicles has been seen in animal studies [42] *Offer sperm banking if patient desires* <u>Female</u> • No data available *Offer egg or embryo freezing if patient desires*	<u>Male and Female</u> • No data available *Contraception throughout treatment and for one year after treatment*	• Pregnancy category D [45] • May cause fetal harm if administered during pregnancy [42, 45] *Pregnancy should be avoided during treatment* [45]	• It is not known whether this drug is excreted in human milk [45] *Should not be used by nursing women* [42, 45]
Gemcitabine (Gemzar®) – antimetabolite	<u>Male</u> • This class of medication typically causes only temporary reduction in sperm production [43] • Decreased sperm production in animal studies. [46] *No need to sperm bank unless patient desires to father a child in the near future and interruption of treatment would not be possible* <u>Female</u> • Defective egg production, menstrual dysfunction, and infertility have been reported [43] • In studies of female mice, fertility was not affected. [46] *No need to freeze eggs or embryos unless patient desires*	<u>Male and Female</u> • No data available *Contraception throughout treatment and for one year after treatment*	• Pregnancy category D [42, 46] • Causes birth defects and pregnancy loss in animals; may cause fetal harm if administered during pregnancy [42, 46] *Pregnancy should be avoided during treatment*	• It is not known whether this drug is excreted in human milk [42, 46] *Should not be used by nursing women,* [42, 46]

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Systemic Chemotherapy and Radiation Therapy				
Exposure to chemotherapeutic agents or radiation can cause mutations in sperm or eggs and birth defects in a developing fetus. [39] It is important to avoid getting pregnant or fathering a baby during treatment, and for a period after treatment. The amount of time to wait will vary based on individual patient and treatment factors. To allow for potentially damaged sperm or eggs to be cleared or repaired before attempting to have a baby, at least six to 12 months wait after treatment is recommended. [40, 41] In addition, women may be advised not to become pregnant during the time at which they are at highest risk for relapse or recurrence. [41]				
Brentuximab Vedotin (Adcetris®) – Antibody Drug Conjugate	<u>Male</u> • No human data but injury to testicles and decreased sperm production has been seen in animal studies. [47] *Offer sperm banking if patient desires future children* <u>Female</u> • No data available *No need to freeze eggs or embryos unless patient desires*	<u>Male and Female</u> • Causes birth defects and pregnancy loss in animals [47] *Contraception throughout treatment and for six months after treatment*	• Pregnancy category D [47] • Causes birth defects and pregnancy loss in animals. [47] *Pregnancy should be avoided during treatment*	• It is not known whether this drug is excreted in human milk [47] *Should not be used by nursing women.*
Pembrolizumab (Keytruda®) – Anti-PD-1 Monoclonal Antibody	<u>Male</u> • No data available *No need to sperm bank unless patient desires* <u>Female</u> • No data available *No need to freeze eggs or embryos unless patient desires*	<u>Male and Female</u> • Based on the way this type of drug works, there is a potential for harm. [48] *Contraception throughout treatment and for four months after treatment*	• Pregnancy category D [48] • Increased the risk of developing immune mediated disorders P*regnancy should be avoided during treatment*	• It is not known whether this drug is excreted in human milk [48] *Should not be used by nursing women*

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Systemic Chemotherapy and Radiation Therapy				
Exposure to chemotherapeutic agents or radiation can cause mutations in sperm or eggs and birth defects in a developing fetus. [39] It is important to avoid getting pregnant or fathering a baby during treatment, and for a period after treatment. The amount of time to wait will vary based on individual patient and treatment factors. To allow for potentially damaged sperm or eggs to be cleared or repaired before attempting to have a baby, at least six to 12 months wait after treatment is recommended. [40, 41] In addition, women may be advised not to become pregnant during the time at which they are at highest risk for relapse or recurrence. [41]				
Total/Partial Skin Electron Beam Therapy	<u>Male and Female</u> • Total skin electron beam therapy delivers a prescribed radiation dose to a depth of only a few mm into the body. There is the potential for minimal x-ray total body exposure to radiation, at most 1% to 2% of the prescribed dose. [49] <u>Male</u> • Because of the proximity of the testes to the scrotal skin, radiation in that area may cause damage to sperm and the cells that produce sperm. [49][43] *Offer sperm banking* <u>Females</u> • Based on the location of the ovaries, there would be no expected effect on eggs or the cells that make eggs. [49] *No need to freeze eggs or embryos unless patient desires*	<u>Male</u> • *See information in Fertility Effects Section.* Because of the proximity of the testes to the scrotal skin, radiation in that area may cause damage to sperm and the cells that produce sperm. These effects may be magnified in patients receiving a boost dose of radiation near the scrotum. [49] *Contraception throughout treatment and for one year after treatment* <u>Female</u> • No data available *Contraception throughout treatment and for one year after treatment*	• No data available *Pregnancy should be avoided during treatment*	• No data available

Definition of Pregnancy Categories [50]

- **Category A -** Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
- **Category B -** No evidence of risk in humans. Either animal study shows risk, but human findings do not; or, if no adequate human studies have been performed, animal findings are negative for risk.
- **Category C -** Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify potential risk.
- **Category D -** Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
- **Category X -** Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports, have shown fetal risk, which clearly outweighs any possible benefit to the patient.

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Fertility Chart Contributors

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