



# Lynch syndrome, endometrial cancer, and fertility-sparing treatment

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Endometrial cancer is one of the most common gynecological cancer in developed countries. It is estimated that more than 65,000 new cases will be diagnosed in the year 2020, in the United States (1,2). Estimated endometrial cancer-related mortality increased dramatically in the last decade, from 7,950 deaths in the year 2010 to 12,590 deaths in the year 2020 (1,2). Endometrial cancer is characterized by an overall good prognosis, with a five-year survival rate of 80% for patients following appropriate treatment (3). Increasing in age and body mass index as well as long-term estrogen exposure are the main factors for developing endometrial cancer (3). Interestingly, endometrial cancer might be due to a genetic predisposition. Overall, hereditary causes contribute to 2–10% of endometrial cancer cases (4). Lynch syndrome is an autosomal dominant genetic disorder characterized by a high risk of developing cancer, in particular colorectal and endometrial cancer. Lynch syndrome is caused by the presence of a germline pathogenic variant in 1 of the 4 DNA mismatch-repair (MMR) genes [*mutL homolog 1 (MLH1)*, *mutS homolog 2 (MSH2)*, *mutS homolog 6 (MSH6)*, or *postmeiotic segregation increased 2 (PMS2)*] (5).

Accumulating evidence highlighted that fertility-sparing option might be offered to young women affected by endometrial hyperplasia and endometrial cancer (6). The antagonism given progesterone might reverse cancerogenic mechanisms. However, in Lynch syndrome patients, the mechanisms on the basis of cancerogenesis are different from what observed in sporadic cases. Guidelines do not recommend the routine adoption of fertility-sparing approach in patients with Lynch syndrome (4,5). However,

growing evidence suggested that progestin therapy is effective even in patients with Lynch syndrome (6). However, we have to underline that molecular mechanism causing disease in patients with Lynch syndrome differ from molecular mechanisms occurring in sporadic cases. Therefore, progestin therapy has a limited value on patients harboring MMR (5). Patients have to be counseled about the risk of developing recurrence/persistence of disease. Additionally, patients with Lynch syndrome are at risk of developing ovarian cancer (4). Diagnostic laparoscopy should carry out in order to exclude possible synchronous malignancies. After patients completed their childbearing desire, hysterectomy is strongly recommended (7).

There is no evidence suggestive that routine testing for progestin receptor is mandatory in patients with Lynch syndrome, since those patients are generally affected by well differentiated tumors. However, testing for estrogen and progestin receptor is recommended.

Patients with Lynch syndrome are at high risk of developing well differentiated endometrioid endometrial cancer (generally expressing estrogen and progestin receptor). But they can be affected also by non-endometrioid endometrial cancer (5). Our study group investigated outcomes of non-endometrioid endometrial cancer suggesting that patients with Lynch syndrome and non-endometrioid endometrial cancer are characterized by better prognosis in comparison to sporadic non-endometrioid endometrial cancer (4). However, no evidence supports the adoption of fertility sparing surgery in poorly differentiated tumor. Patients with Lynch syndrome are at high risk of developing ovarian malignancies.

The risk of having synchronous malignancies would be considered. Owing the risk of occult malignancy not detectable by visit and ultrasound patients should have laparoscopic assessment of the ovary and peritoneal cavity. There is no evidence supporting the routine use of ovarian biopsies. Additionally, genetic consultation is strongly recommended, since patients should know the risk of transmission of Lynch syndrome to the newborn. To date, no data support the use of prophylactic surgery in endometrial cancer patients managed conservatively. However, Lynch syndrome patients are at high risk of developing new endometrial lesions. Basically, due to genetic mechanism at the basis of cancerogenesis. Therefore, patients should be counseled to have prophylactic risk reduction surgery (7). Further evidence is necessary to assess the safety and long-term effectiveness of fertility-sparing treatment in patients with Lynch syndrome. Adequate counseling should be carried out. Patients should be informed about the risk of omitting radical procedures.

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