Fertility Challenges Facing Women with Early-Stage Endometrial Cancer

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Abstract

Young women diagnosed with endometrial cancer may have a fertility wish and may, under certain conditions, be offered fertility-sparing treatment. However, they may also have underlying infertility issues, as anovulation, obesity, polycystic ovary syndrome, and advanced maternal age are often found in women with endometrial cancer or atypical hyperplasia. These fertility issues may hinder pregnancy or prolong the time to pregnancy, in a situation where not much time is allowed to try for a pregnancy. Referral to a reproductive specialist is recommended as early as possible to detect any possible underlying infertility issues that might require assisted reproductive technology once a pregnancy is allowed or may even contradict fertility-sparing treatment. Ovarian reserve testing is a tool used to assess a woman's ovarian reserve, although it cannot, as such, be used to predict the chance of pregnancy. In case of obesity, weight loss is recommended as soon as possible.

Keywords

- endometrial cancer
- fertility
- obesity
- ovarian reserve
- PCOS

Recently, fertility-sparing treatment has been offered to women of fertile age with a future pregnancy wish in selected cases and under certain, strict criteria.[1] The standard treatment for endometrial cancer is total hysterectomy with bilateral salpingo-oophorectomy, but if the cancer is early-stage and nonmetastatic or atypical hyperplasia, nonsurgical treatment with hysteroscopic tumor resection followed by hormonal treatment with oral progestins and/or a levonorgestrel-releasing intrauterine device can be an alternative. This will potentially allow for a future pregnancy once the patient has reached complete response. However, the window in which the patient is allowed to become pregnant is short, and ultimately definitive surgery is recommended. The purpose of this article is to highlight and discuss some of the fertility-related problems women are faced with and how to address them.

Background

Endometrial cancer is not the most common type of cancer found in women with an age-standardized incidence of 12.8/100,000 women in the Nordic countries,[2] but the incidence is increasing, and although not often affecting young women, it does occur even in the age group younger than 40 years. For atypical hyperplasia, the incidence is also very low in women of fertile age with a rate of less than 7 cases per 100,000 women in their 30s per year.[3] And for this age group, it can have devastating consequences, because of the profound effects it can have on fertility. With the increasing trend to postpone childbearing and the increasing age of first child, which is seen in the industrialized world, the chance of a woman being nulliparous when diagnosed with endometrial cancer or atypical hyperplasia is high. Infertility is seen more often in obese women and women diagnosed with polycystic ovarian syndrome (PCOS) than in normal weight and regularly cycling women, as is endometrial cancer. So even though a lot of these women will have a pregnancy wish and will be candidates for fertility-sparing surgery, they may, as illustrated in ►**Fig. 1**, face problems in becoming pregnant, which will be discussed in this article.

Ovarian Reserve Assessment

Before the decision is made to offer fertility-sparing treatment, the patient should be referred to a fertility specialist

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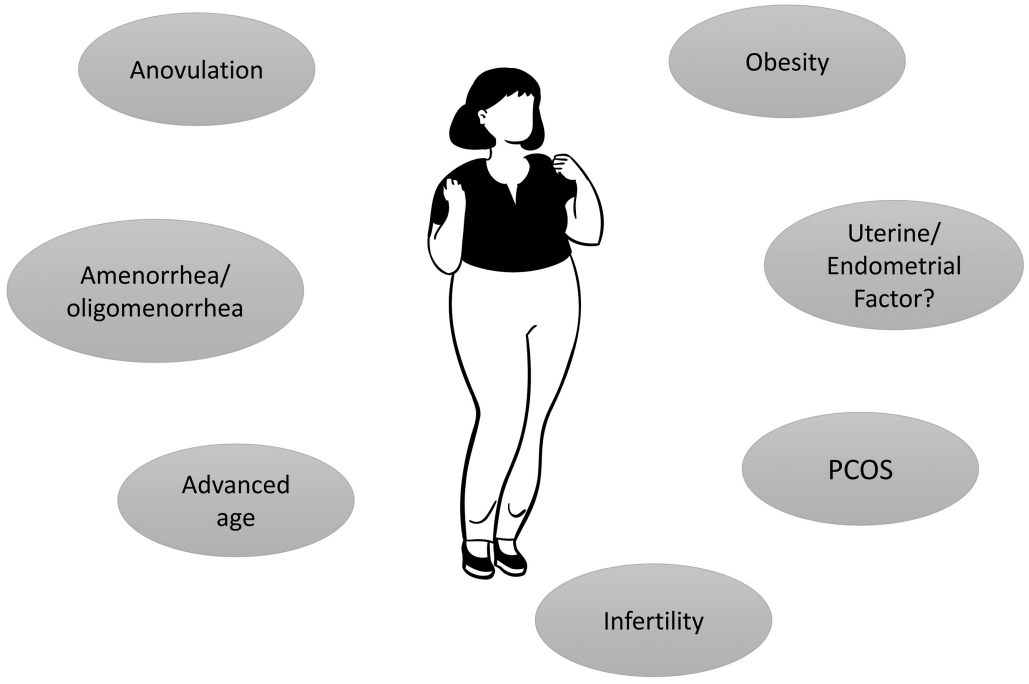

Fig. 1 Fertility challenges facing women with endometrial cancer.

for fertility assessment and individual counseling. Many factors can contribute to an individual's fertility, and if the chance of pregnancy is already found to be very low, she may be better off going directly for standard surgical treatment. If, on the other hand, the patient does not have too many risk factors associated with low fertility and she otherwise fulfills the criteria, fertility-sparing treatment can be considered.

Menstrual Cycle Length

Regular menstrual cycles lasting 28 to 31 days are strong indicators of spontaneous ovulation and a well-functioning hypothalamic–pituitary–gonadal axis, suggesting a good chance of natural conception. However, women with PCOS often have anovulatory cycles or infrequent ovulation, leading to amenorrhea or oligomenorrhea.[4] This means that her chances of conceiving spontaneously each month are severely reduced, and time to pregnancy will often be much longer than for regularly cycling women. This can be a problem if a short time-to-pregnancy is required. Nevertheless, for women with PCOS there is a trend toward more cycle regularity with age, which could improve their fertility, although the oocyte quality remains the same as for the same-age background population. It is normal for the menstrual cycle to shorten in the years leading up to the perimenopausal transition, and this can serve as an early sign of declining ovarian reserve. As menopause approaches, cycles become irregular and eventually stop. A recent systematic review and meta-analysis found that shorter menstrual cycles (21–27 days), compared with normal cycles (28–31 days), were significantly associated with lower anti-Müllerian hormone (AMH) levels, lower antral follicle count (AFC), reduced fecundability, and poorer in vitro fertilization (IVF) outcomes.[5]

Basal Serum Follicle-Stimulating Hormone and Estradiol Measurement

Early-follicular-phase measurement of follicle-stimulating hormone (FSH) can be used to detect a diminished ovarian reserve. Elevated levels on days 2 to 5 of the menstrual cycle are a specific, but not sensitive test for a reduced ovarian reserve, but with significant inter- and intracycle variability. Basal estradiol (E_2) measurement can be used as an aid to interpret the basal FSH value correctly. An early rise in serum E_2 concentrations is seen in women with a diminished ovarian reserve, but will cause the FSH level to drop from an elevated level to within the normal range, so a normal FSH value concomitant with an elevated E_2 concentration may still indicate a diminished ovarian reserve. However, the Practice Committee of the American Society for Reproductive Medicine states that ovarian reserve tests are poor predictors of reproductive potential independently from age and should only be used as predictors of oocyte yield following controlled ovarian stimulation.[6]

Anti-Müllerian Hormone

AMH is a member of the transforming growth factor-β superfamily and is produced by the granulosa cells of preantral and small antral follicles. It has long been recognized as one of the best predictors we have for ovarian reserve, albeit not perfect. After its peak values around 25 years of age, a gradual decline of around 5% per year is seen.[7] AMH is one of the biomarkers used in the Bologna criteria for low ovarian reserve and, more recently, in the Poseidon criteria for identifying patients who have a low prognosis in assisted reproductive technology (ART). According to the Bologna criteria, a low ovarian reserve is defined as having at least two of the following three criteria: (1) an advanced maternal age, (2) a previous poor ovarian response to ovarian

stimulation, (3) an abnormal ovarian reserve test defined by an AFC of less than five to seven follicles or an AMH level less than 0.5 to 1.1 ng/mL.[8] In the Poseidon criteria, four groups of low prognosis patients are defined, and AMH occurs in all four definitions: group 1 includes young patients with a suboptimal/low oocyte number, group 2 includes old patients with a suboptimal/low oocyte number, group 3 includes young patients with an expected low oocyte number, and group 4 includes old patients with an expected low oocyte number. Here, a low AMH is defined as less than 1.2 ng/mL.[9]

Several studies have looked at the role of AMH in predicting outcomes after ART. One meta-analysis that included 32 studies analyzed the relationship between AMH and cumulative live birth rate (CLBR) after ART.[10] The authors found that serum AMH levels were linked to CLBR, although no discriminating lower or upper threshold could be established, prompting the authors to discourage the use of AMH as the sole criterion for rejecting IVF treatment. No predictive value between AMH and clinical outcomes after intrauterine insemination (IUI) could be found. Tal and co-authors found that the predictive ability for AMH and pregnancy was greatest in women with a diminished ovarian reserve with an odds ratio (OR) of 3.96 (95% confidence interval [CI]: 2.57–6.10).[11] The consequences of having a high AMH, which is the case for women with PCOS, have also been assessed in relation to ART. A meta-analysis demonstrated that women with PCOS and an AMH within the 75th to 100th percentile had a decreased odds of a clinical pregnancy (OR: 0.77, 95% CI: 0.63–0.93) and livebirth (OR: 0.71; 95% CI: 0.58–0.87) when compared with those within the lowest percentiles.[12] In this study, the authors also looked at the number of oocytes retrieved and fertilization rate, and although there was an increased number of oocytes retrieved in the high AMH group, the fertilization rate was decreased.

In non-PCOS women, on the other hand, AMH has been shown to be a poor predictor of the chance of natural conception, even in women with a low AMH value.[13,14]

Antral Follicle Count

Another biomarker of ovarian reserve is the AFC. Antral follicles between 2 and 10 mms in size are counted and the number has been found to be closely related to the total number of primordial follicles in the ovaries.[15] A linear relationship of AFC with age has been demonstrated with a median decline of 2.4% per year in 362 regularly cycling premenopausal women.[16] This was confirmed by Bentzen and co-authors who found that chronological age was inversely related to total AFC in 366 healthy healthcare workers.[17] An interesting finding from this study was that subclasses of antral follicles sized 2 to 4 and 5 to 7 mm decreased with increasing age, whereas antral follicles sized 8 to 10 mm increased with increasing age, and the occurrence of large follicles was more strongly related to biological age than chronological age. Comparing 228 users of hormonal contraception with 504 non-users, AFC was found to be 30.4% lower in the hormonal contraception group after adjusting for age, calling for caution when interpreting ovarian reserve markers in users of hormonal contraception, which is also the case for AMH.[18] AFC (as AMH) has been found to be a good predictor of the outcome of ovarian stimulation. Two studies have independently found it to be an accurate predictor of excessive response to ovarian hyperstimulation with a sensitivity of 82% and a specificity of 80%[19] and has been suggested ideal, (together with AMH) in planning personalized controlled ovarian stimulation protocols.[20] However, AFC is not a good tool in predicting the chance of pregnancy after IVF, as found in a meta-analysis by Hendriks et al that included 10 studies.[21]

Age

One of the most important predictors of the chance of pregnancy and live birth is the woman's age. This is due to both the declining number of oocytes and the increasing proportion of oocytes with chromosomal abnormalities that occur with advanced age.[22] It has long been known that as women age, endocrine changes will occur concomitant with cycle irregularities, eventually leading to menopause.[23] A systematic review and individual participant data meta-analysis that included 4,379 women of at least 35 years of age revealed an expected natural fertility decline with female age. The probability of natural conception significantly decreased with any diagnosis of infertility, when compared with unexplained infertility.[24] Embryo aneuploidy is considered the most important limiting factor in the success rates after ART. But even after performing preimplantation genetic testing for aneuploidy and only transferring euploid embryos, there is a reduced ongoing pregnancy rate (OPR) and live birth rate (LBR) among women older than 35 years. A recent systematic review and meta-analysis found a higher OPR/LBR (OR: 1.29; 95% CI: 1.07–1.54) in women <35 years than in women ≥ 35 years with a risk difference equal to 0.06 (95% CI: 0.02–0.09), suggesting that other factors as well play a part in the reduced chance of a live birth in older women.[25] This is supported by a retrospective cohort study evaluating implantation rate (IR) after 8,175 euploid embryo transfers from a single center. All women had single embryo transfer, and prior to transfer all women underwent uterine cavity evaluation to exclude any anatomical abnormalities. Patients were divided into five age groups: <35 years old ($n = 3,789$ embryos transferred), 35 to 37 ($n = 2,200$), 38 to 40 ($n = 1,624$), 41 to 42 ($n = 319$), and >42 ($n = 243$). Again, the authors found that IR negatively correlated with age. Women 38 years or older had a significantly lower IR than those under 35 (OR: 0.85, 95% CI: 0.73–0.99 for 38–40 years old; 0.69, 0.53–0.91 for 41–42, and 0.69, 0.51–0.94 for >42).[26]

Another factor to consider when explaining the reduced fertility that comes with advanced maternal age is the endometrium and its ability to allow for implantation and sustain a pregnancy. Studies have shown that there might be an association between a decline in endometrial receptivity and advanced maternal age.[27] In an oocyte donation program

using either intended parent recipients or gestational carriers, the odds of a clinical pregnancy were significantly higher when using a gestational carrier (65.2 vs. 56.3%, adjusted OR [aOR]: 1.33, 95% CI: 1.17–1.51), which was also the case for live birth (57.1 vs. 46.4%, aOR: 1.37, 95% CI: 1.21–1.55).[28] But further studies are needed.

Together, all these studies show that age is an important factor to take into consideration before offering fertility-sparing treatment to women with early-stage endometrial cancer, even if they want to use donor eggs.

Obesity

Overweight and obesity are an increasing problem all over the world. It affects nearly two in five adults globally and is no longer a problem solely concerning the industrialized world.[29] It has huge economic- and health-related consequences, not only on an individual basis but also for the society. It contributes to numerous diseases, including cancer. With this growing trend of more and more people becoming obese, particularly among the younger population, more cases of endometrial cancer are to be expected in women of fertile age in the future. Obesity also affects fertility. The ovarian reserve markers AMH and AFC have been found to be significantly lower in obese women when compared with non-obese women, indicating reduced fertility.[30] A very recent systematic review and meta-analysis found that female overweight and obesity are associated with an increased risk of subfecundity (OR = 1.44; 95% CI: 1.20, 1.72) and infertility (OR = 1.60, 95% CI: 1.31–1.94).[31] And it does not seem that ART can circumvent this. Turner et al found in their meta-analysis that overweight and obese women, who were otherwise healthy and with no comorbidities, still were less likely to attain a clinical pregnancy, if their BMI was >25 (OR: 0.76, 95% CI: 0.62–0.93, $p = 0.007$), and even more so with a BMI >30 (OR: 0.61, 95% CI: 0.39–0.98, $p = 0.04$) when using ART.[32] They also required more days of stimulation and achieved fewer oocytes than women with a normal BMI. Other studies support these findings.[33,34]

The Role of Lifestyle Change

With the knowledge we have of reduced fertility in overweight and obese women, it is obvious to encourage lifestyle changes. Measures such as reduced caloric intake, healthier diet, increased aerobic exercise, and adaptation to a less sedentary lifestyle should be encouraged as the first choice. However, these measures do not always lead to the desired weight loss and can sometimes be difficult to adhere to in the long run. A prospective, randomized controlled trial including 317 women < 38 years of age with a BMI of >30 and <35 from Denmark, Iceland, and Sweden found no statistically significant difference in LBR between those randomized to weight reduction on a low-caloric diet 3 months prior to IVF and the control group without weight loss.[35] Modern weight loss drugs such as the glucagon-like peptide-1 receptor agonists (GLP-1) or bariatric surgery may be an alternative. Although for obese patients, lifestyle intervention studies leading to weight loss have many beneficial consequences to their general health, there seems to be little to no effect on fertility for some reason.[36–38] In any case, patients with endometrial cancer who have obtained complete remission rarely have the time to lose weight before trying to conceive; so, lifestyle advice should ideally be given at the time of diagnosis rather than at the time of complete remission.

Polycystic Ovarian Syndrome

PCOS is a condition defined by ovulatory dysfunction causing irregular menstrual cycles, hyperandrogenism, and polycystic ovaries (at least two of these three criteria should be present) according to the Rotterdam criteria.[39] It is believed to affect 5 to 20% of reproductive-aged women worldwide. Although not perfect, recent guidelines and reviews still recommend using the Rotterdam criteria in the diagnosis of PCOS.[40,41] In general, women with PCOS are found to have higher levels of serum AMH and higher AFC than women not diagnosed with PCOS, indicating a higher ovarian reserve[42]; however, as discussed above, this is not always an advantage when a short time to pregnancy is desired. A higher risk of developing endometrial cancer has been found in women with PCOS.[43] Factors such as elevated estrogen for a longer period of time, type-2 diabetes, obesity, and persistent thick endometrium, all associated with PCOS, can all individually act as risk factors for developing endometrial cancer. However, one study found that when adjusting for BMI, the association between PCOS and endometrial cancer was no longer found.[44] A recent comprehensive review on the endometrial function of women with PCOS found evidence to support the presence of an "endometrial factor" related to subfertility and poor pregnancy outcomes in these women.[45] This can in part be explained by the hyperestrogen and hyperandrogen responsiveness of the endometrium and the progesterone resistance on top of an inhospitable and inflammatory environment leading to abnormal trophoblast invasion and placentation, miscarriage, and pregnancy complications.

Use of Metformin

Metformin is an antihyperglycemic biguanide drug used in the treatment of type 2 diabetes mellitus. It inhibits hepatic gluconeogenesis and reduces the action of glucagon, thus reducing the levels of circulating insulin and glucose. This could be beneficial for women with PCOS, as their increased insulin resistance, hyperandrogenism, and obesity all have an impact on menstrual cyclicity and thus fertility. The hope is that treating women with PCOS with metformin will lead to more ovulatory cycles and increase the chance of natural conceptions. A Cochrane review found that metformin may improve LBRs compared with placebo (OR: 1.59, 95% CI: 1.00–2.51). The metformin group had higher rates of clinical pregnancies (OR: 1.93, 95% CI: 1.42–2.64), ovulation (OR: 2.55, 95% CI: 1.81–3.59), and menstrual frequency (OR: 1.72, 95% CI: 1.14–2.61).[46] In non-obese women with PCOS, treatment with metformin also seems to have some effect on the clinical pregnancy rate. A systematic review and meta-analysis of 21 RCTs including 2638 normal-weight women with

PCOS found a slight increase in clinical pregnancy rate compared with placebo (47.7 vs. 42.9%) (pooled risk ratio = 1.08 [0.82, 1.42], 95% CI, $p = 0.60$), results being comparable to clomiphene citrate.[47]

An alternative use of metformin is to reverse endometrial hyperplasia, although the evidence of its beneficial effect remains uncertain. In a Cochrane review, the authors found insufficient evidence to support or refute the use of metformin in the treatment of atypical endometrial hyperplasia, calling for better-designed randomized controlled trials with long-term outcome.[48]

Lynch Syndrome

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, is a hereditary autosomal dominant disorder that increases the risk of many types of cancer such as endometrial cancer. Women with Lynch syndrome have a higher overall risk of developing cancer than men, and some of these women will still be of reproductive age and wish a pregnancy. However, the risk of passing on the gene to a child is of great concern, and for some preimplantation genetic testing for monogenic/single-gene disorders (PGT-M) could be an option.[49] Obviously, women carrying the gene should ideally become pregnant before the onset of a cancer, but the condition is often underdiagnosed, which could explain the so far low use of PGT-M for this specific condition. But PGT-M can be time-consuming, and, as such, may not be a realistic option for patients already diagnosed with endometrial cancer.

Conclusion

Young women diagnosed with early-stage endometrial cancer or atypical hyperplasia are often also challenged with factors predisposing to infertility or subfertility. This can further complicate their chances of conceiving in the short period after complete remission has been obtained, during which they are allowed to become pregnant. PCOS is associated with an increased risk of endometrial cancer, and with PCOS there is an increased risk of anovulation and obesity. This may require the use of ART to shorten the time to pregnancy, but even with ART the pregnancy rates and delivery rates are reduced in obese women as compared with normal-weight women. Age is also a risk factor associated with infertility. A reduced ovarian reserve and an increased risk of aneuploidy in the remaining oocytes are seen with increasing age. This reduces the pregnancy rates and delivery rates, something that cannot be compensated by ART. So, in conclusion, women who are candidates for fertility-sparing surgery should be selected carefully, and healthcare professionals should be aware of the underlying infertility issues that these women are often faced with.

Conflict of Interest
None declared.

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