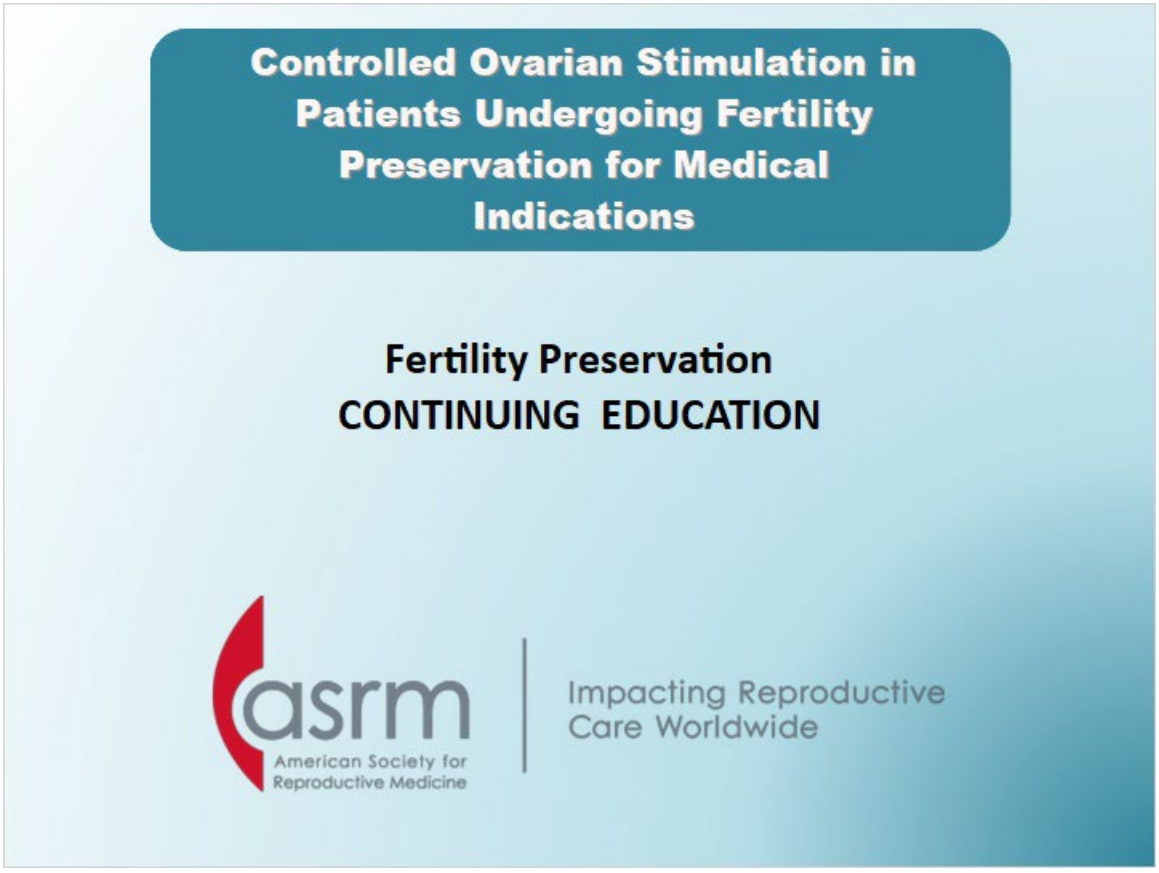
MD120 Lesson 4

1. MD120_L4

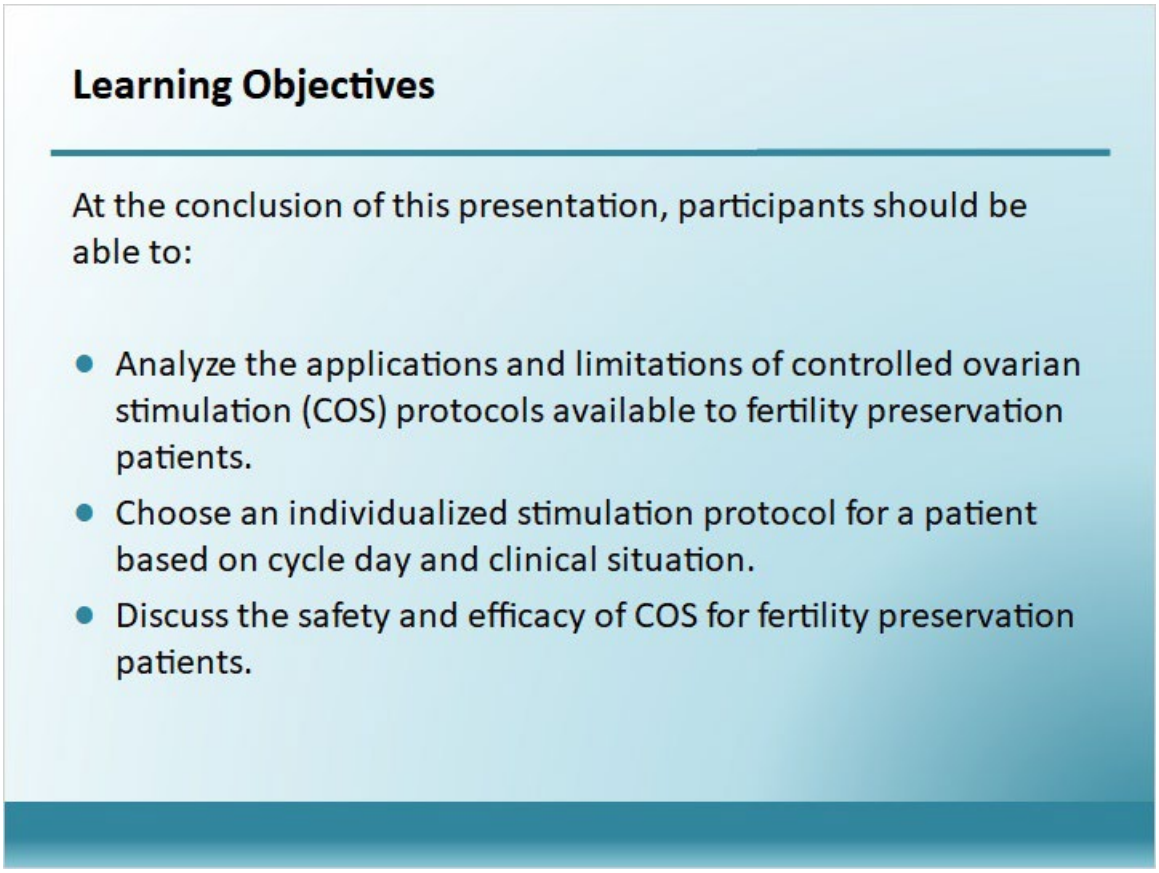
1.1 Controlled ovarian stimulation in patients undergoing fertility preservation for medical indications



Notes:

Welcome to the American Society for Reproductive Medicine's eLearning modules. The subject of this presentation is "Controlled ovarian stimulation in fertility preservation patients."

1.2 Learning Objectives

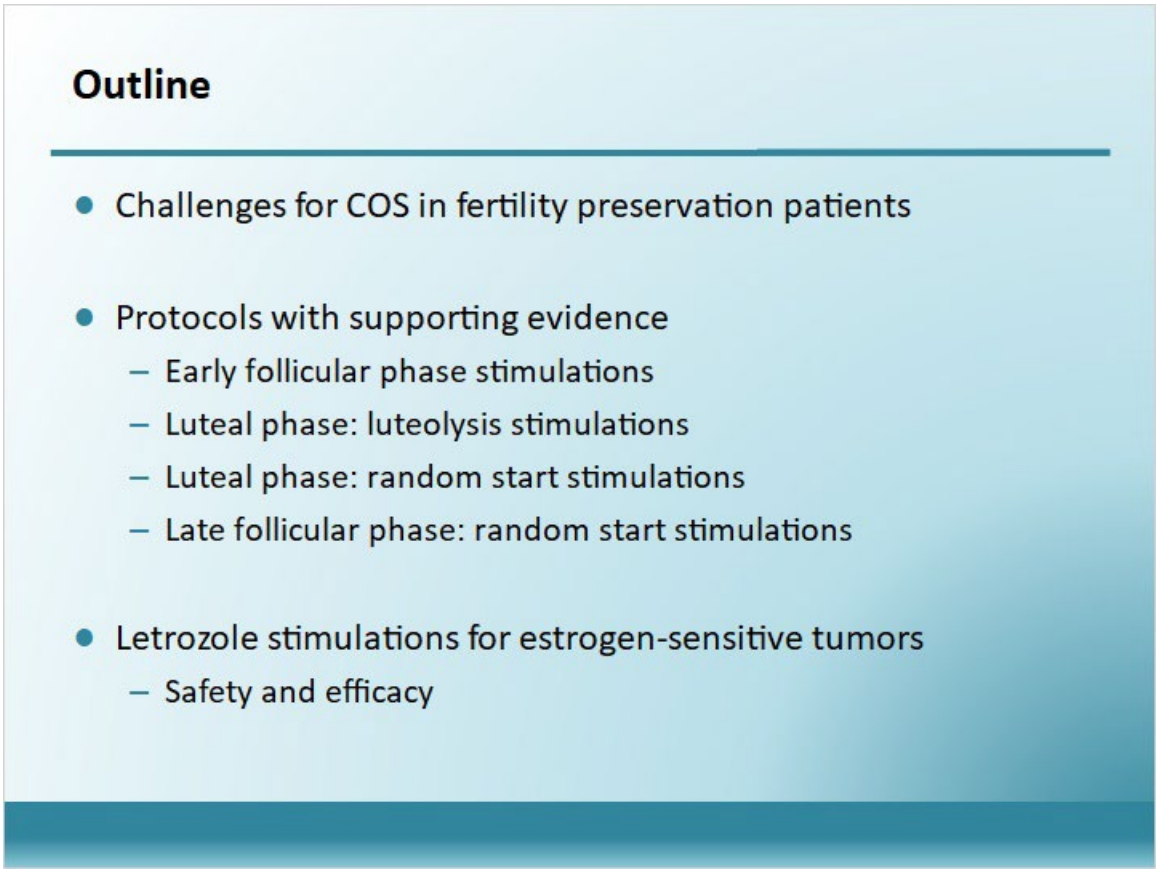


Notes:

At the conclusion of this presentation, participants should be able to:

1. Analyze the applications and limitations of controlled ovarian stimulation protocols available to fertility preservation patients.
2. Choose an individualized stimulation protocol for a patient based on cycle day and clinical situation.
3. Discuss the safety of controlled ovarian stimulation for fertility preservation patients.

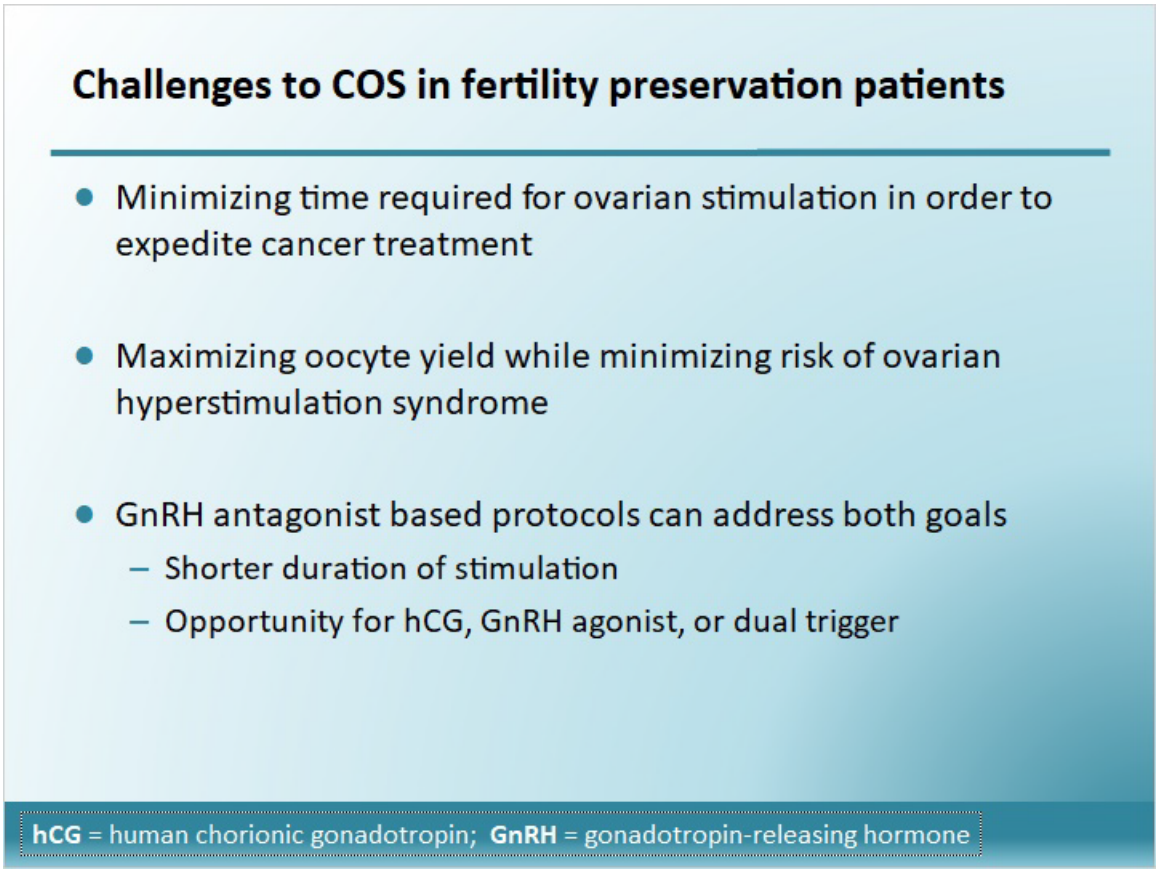
1.3 Outline



Notes:

This module will begin by outlining some of the unique challenges to undertaking controlled ovarian stimulation in fertility preservation patients. The presentation will then review the various options for initiating ovarian stimulation according to the phase of the menstrual cycle in which a patient presents for care - early follicular phase, luteal phase, or late follicular phase. This section will review sample protocols as well as present evidence regarding the outcomes of their use. Finally, the presentation will briefly touch upon the efficacy and safety of ovarian stimulation in women with estrogen-sensitive tumors.

1.4 Challenges to COS in fertility preservation patients

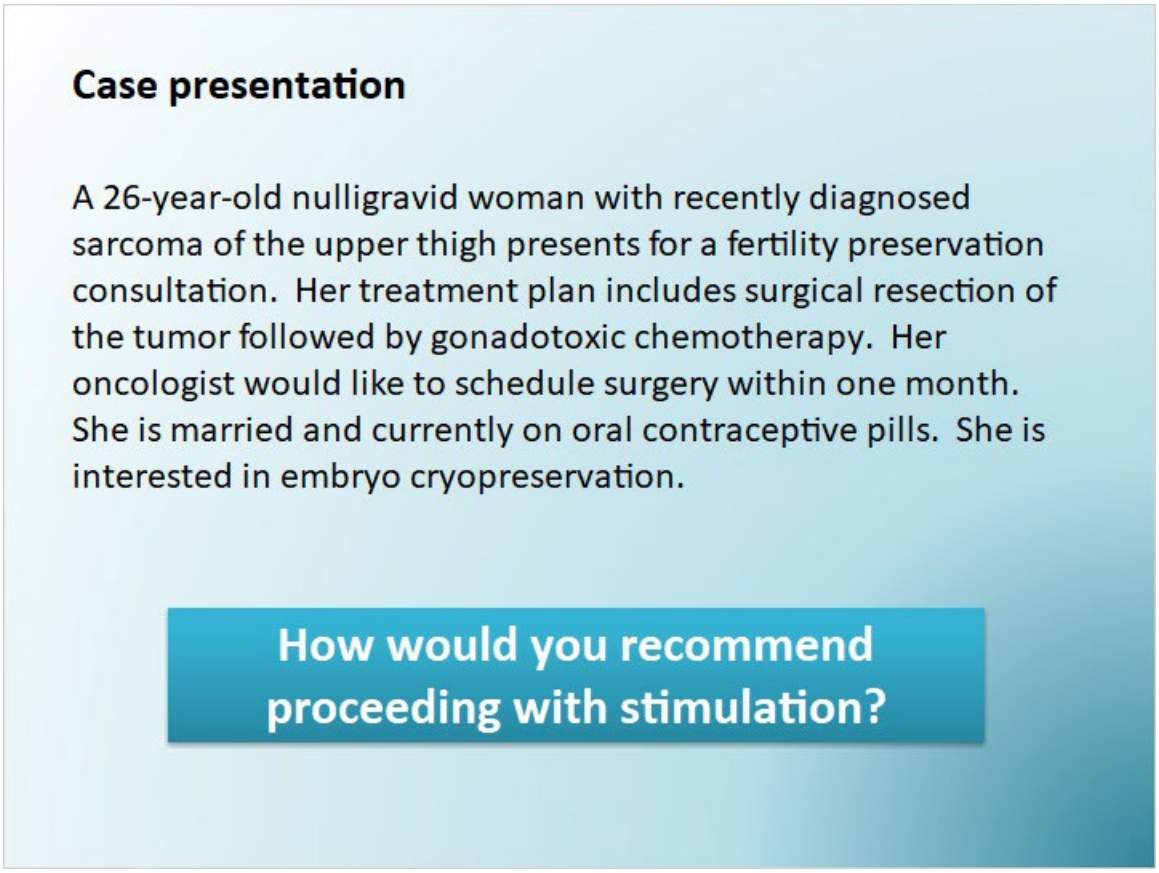


Notes:

Fertility preservation patients undergoing controlled ovarian stimulation pose a number of unique challenges. Many women are not candidates for the 2-6 weeks required for typical downregulation protocols due to a pressing need to start cancer treatment. As exposure to gonadotoxic therapy or the presence of malignancy itself can compromise ovarian reserve, providers must work to maximize response for oocyte or embryo cryopreservation while simultaneously minimizing risk of ovarian hyperstimulation syndrome (OHSS). The latter risk is inherently limited in fertility preservation patients since a fresh embryo transfer is generally not planned.

Use of GnRH-antagonists such as ganirelix and cetrorelix can help expedite controlled ovarian stimulation in fertility preservation patients. A GnRH-antagonist protocol also offers the opportunity to use human chorionic gonadotropin (hCG), a gonadotropin-releasing hormone (GnRH) agonist such as leuprolide, or a combination of both to trigger ovulation, thus further minimizing OHSS risk.

1.5 Case presentation

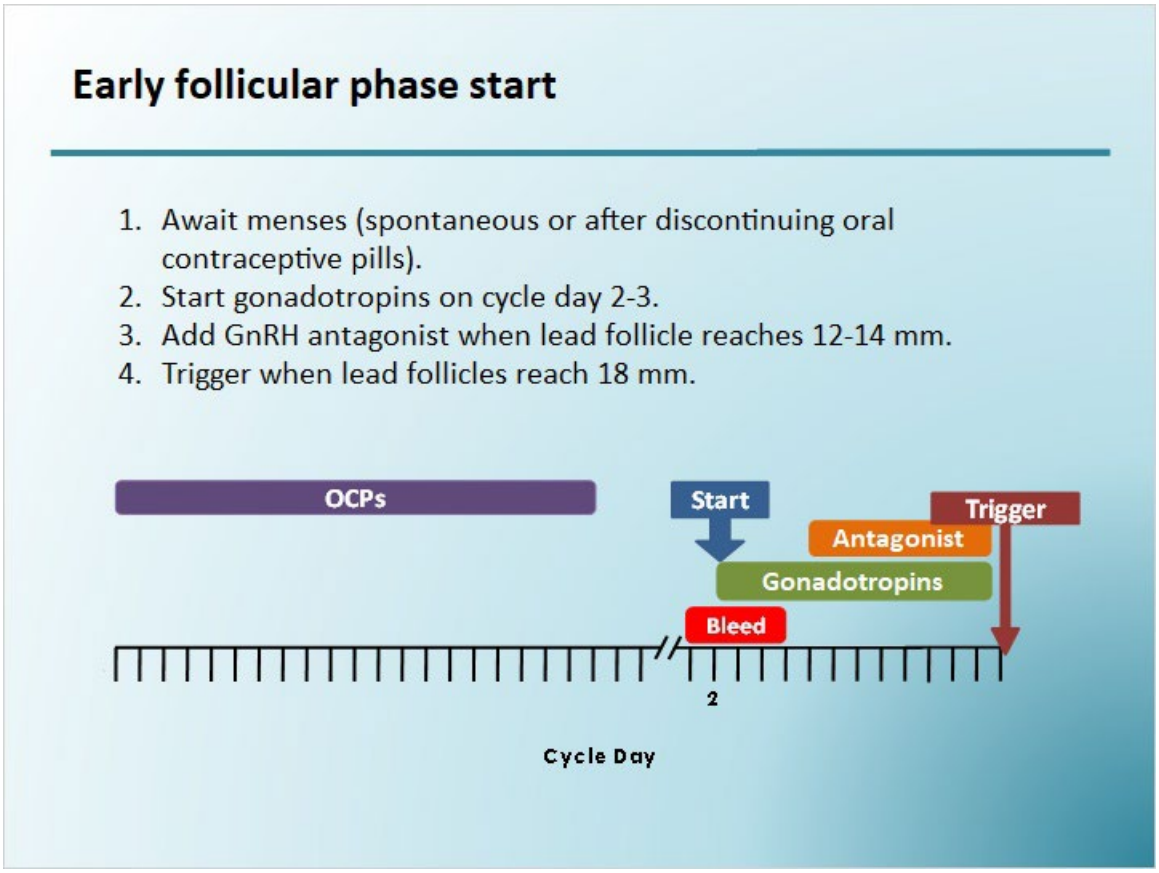


Notes:

The discussion of protocol options begins with a case presentation. This is a 26-year-old nulligravid woman with a recently diagnosed sarcoma of the upper thigh who is planning a surgical resection of the mass, followed by gonadotoxic chemotherapy. She is married and currently uses oral contraceptive pills for contraception. She presents interested in embryo cryopreservation. Her oncologist would like to schedule the surgery within the next four weeks but will accept a brief delay for stimulation.

How would you recommend proceeding with her stimulation?

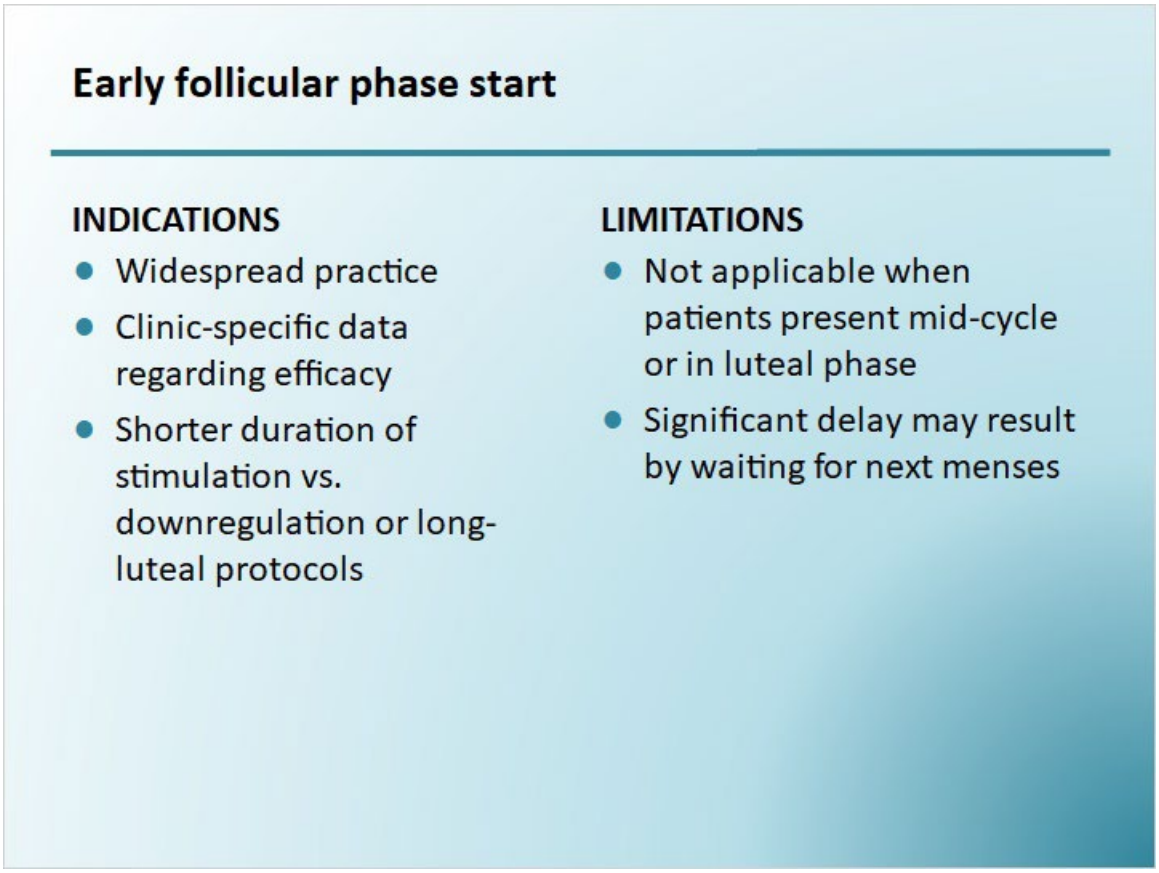
1.6 Early follicular phase start



Notes:

Women who present for fertility preservation in their perimenstrual phase or while on oral contraceptive pills are among the most straightforward to manage as minimal delay is required to await a menses or withdrawal bleed. These patients are typically started on gonadotropins in the early follicular phase, typically cycle days 2-3. If time constraints are significant, stimulation can also be started 2-3 days after discontinuing oral contraceptive pills without awaiting a bleed. A GnRH antagonist is added to prevent a premature luteinizing hormone (LH) surge when the lead follicle reaches 12-14 mm in diameter. Either hCG or a GnRH agonist can be used to trigger ovulation when at least two lead follicles are above 18 mm in diameter.

1.7 Early follicular phase start

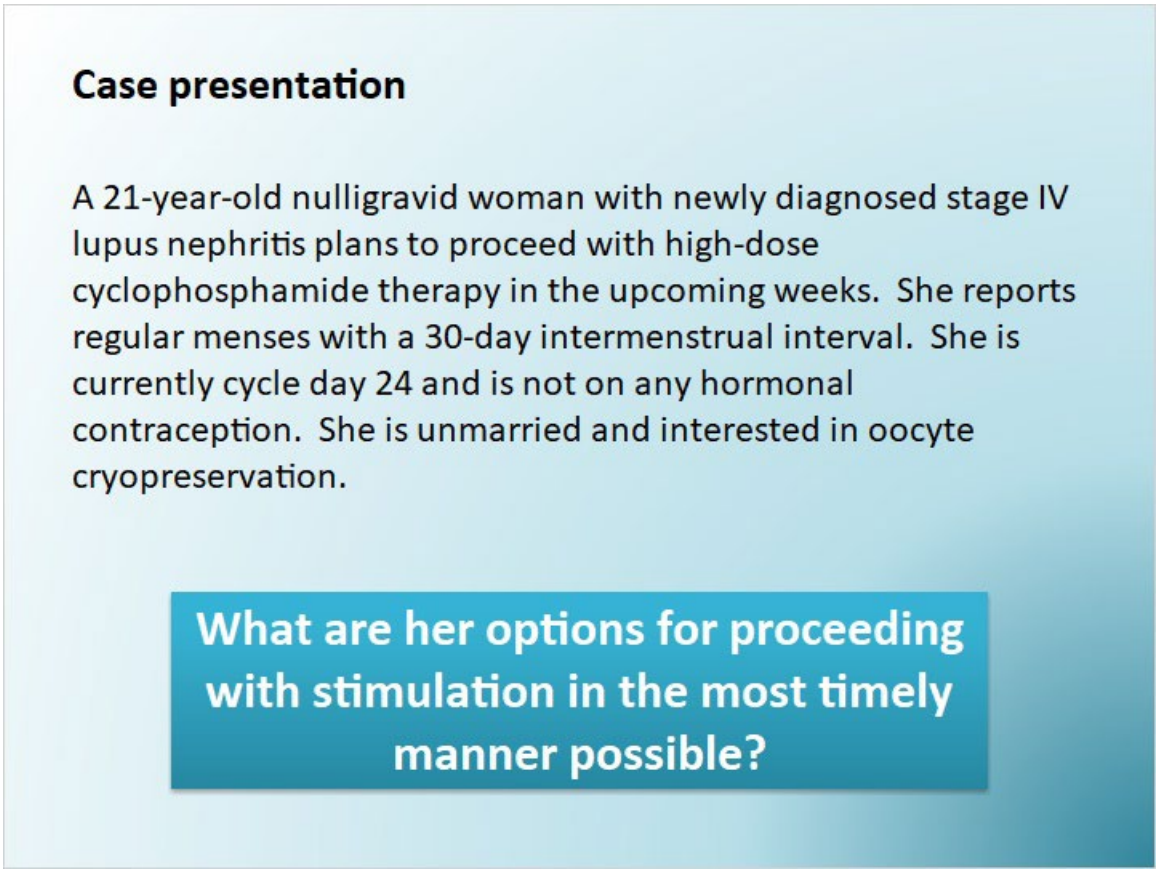


Notes:

Early follicular phase starts using GnRH antagonists are widely used in clinical IVF practice and most clinics will therefore be able to offer clinic-specific data regarding their efficacy. GnRH antagonist protocols are also shorter than downregulation or long luteal protocols, enabling patients to proceed to cancer treatment in an efficient manner.

However, fertility preservation patients may present for evaluation at any point in their menstrual cycle. Strict adherence to a policy of early follicular phase stimulation start may therefore result in significant delay of treatment while awaiting a patient's next menses. Alternatives to an early follicular phase start have therefore been explored.

1.8 Case presentation

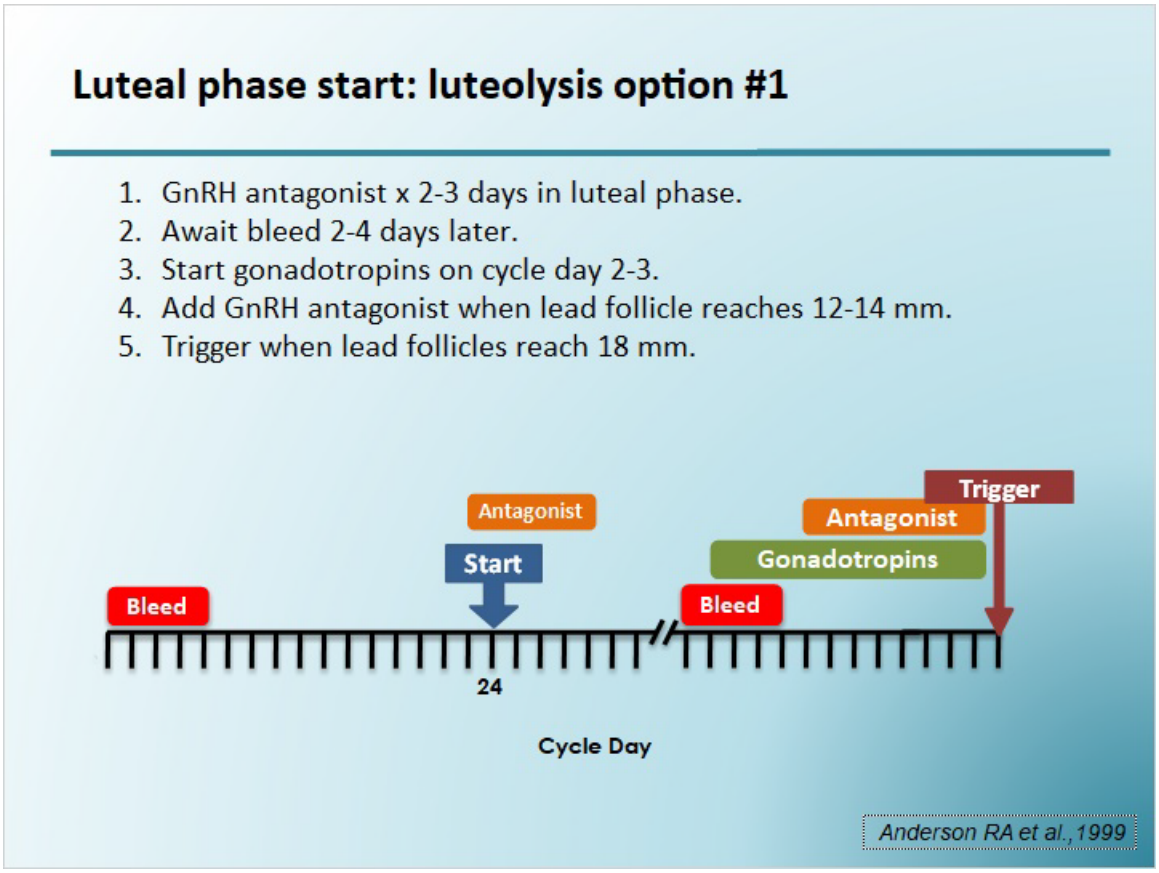


Notes:

The second case is a 21-year-old nulligravid single woman who was recently diagnosed with stage IV lupus nephritis with plans for high dose cyclophosphamide therapy that is likely to be gonadotoxic. She has regular menstrual cycles with a 30-day intermenstrual interval. She is currently cycle day 24 and is not on any hormonal contraception. She is interested in oocyte cryopreservation but her nephrologist would like her to undergo stimulation in as timely a fashion as possible so as to minimize delays to her treatment.

What are her options for proceeding with stimulation in the most timely manner possible?

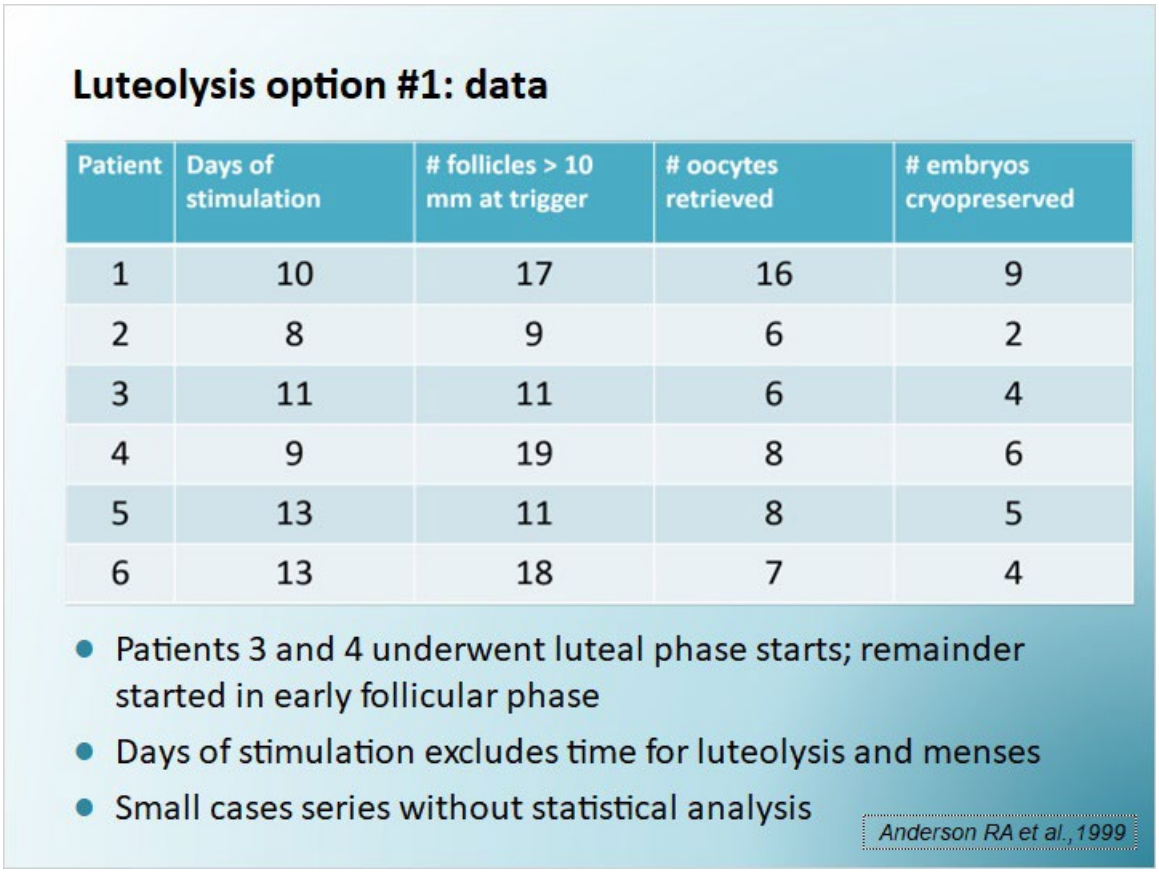
1.9 Luteal phase start: luteolysis option #1



Notes:

Traditional teaching is that luteolysis, or breakdown of the corpus luteum to stop progesterone production, is a requirement for initiating controlled ovarian stimulation in the luteal phase. GnRH antagonists have been explored as a means of luteolysis by several groups. Early studies on the topic suggested a short administration of GnRH antagonists for 2 to 3 days in the luteal phase in order to reduce serum progesterone levels and bring on the onset of menses 2 to 4 days later. Some practitioners may check progesterone levels to confirm luteolysis and start stimulation without awaiting a bleed. The remainder of the cycle would proceed in a fashion similar to a typical GnRH antagonist cycle starting in the early follicular phase.

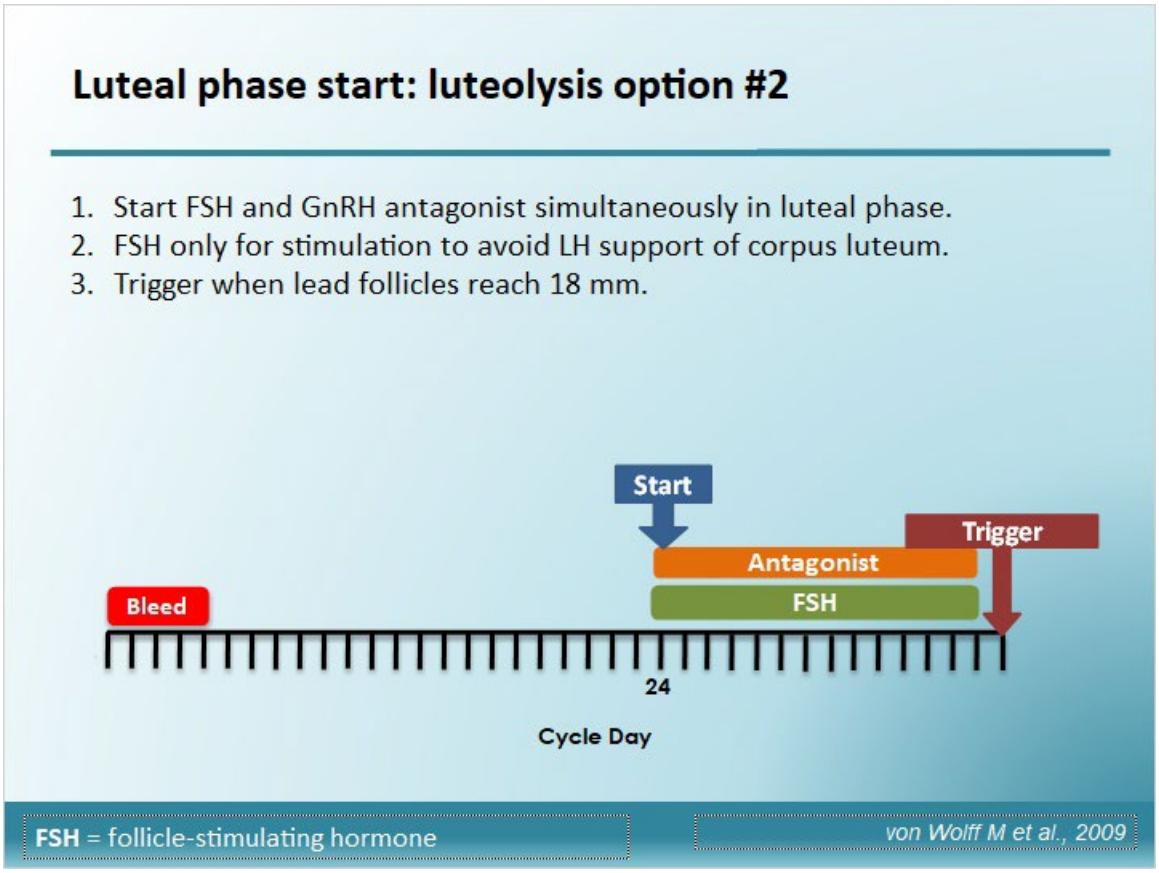
1.10 Luteolysis option #1: data



Notes:

Only a few small case series have reported outcome data with this approach. Data is shown here from a case series of six patients where patients 3 and 4 underwent a luteal phase start and the remaining patients presented and were stimulated in their early follicular phase. Though no statistical analysis was performed, the findings suggest that a synchronized cohort of follicles can develop with grossly normal numbers of oocytes retrieved and embryos cryopreserved. It is worth noting, however, that the days of stimulation do not include the time needed for luteolysis and onset of menses.

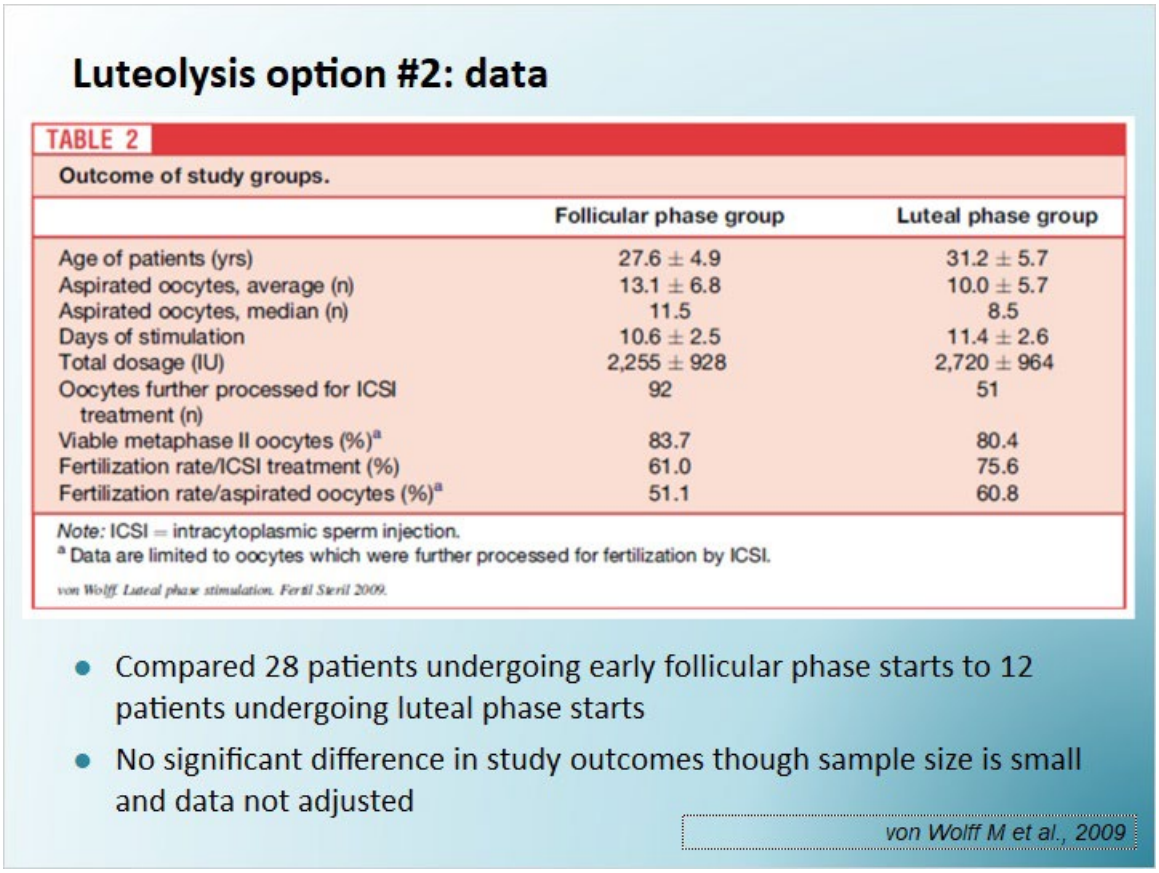
1.11 Luteal phase start: luteolysis option #2



Notes:

A second luteolytic approach is to administer GnRH antagonists and gonadotropins simultaneously during the luteal phase without waiting for a menses. In this protocol, follicle-stimulating hormone (FSH) alone is used for ovarian stimulation due to concern that exogenous LH administration may prevent luteolysis. Although some patients may experience breakthrough bleeding during stimulation, this should not be a concern as no embryo transfer is planned.

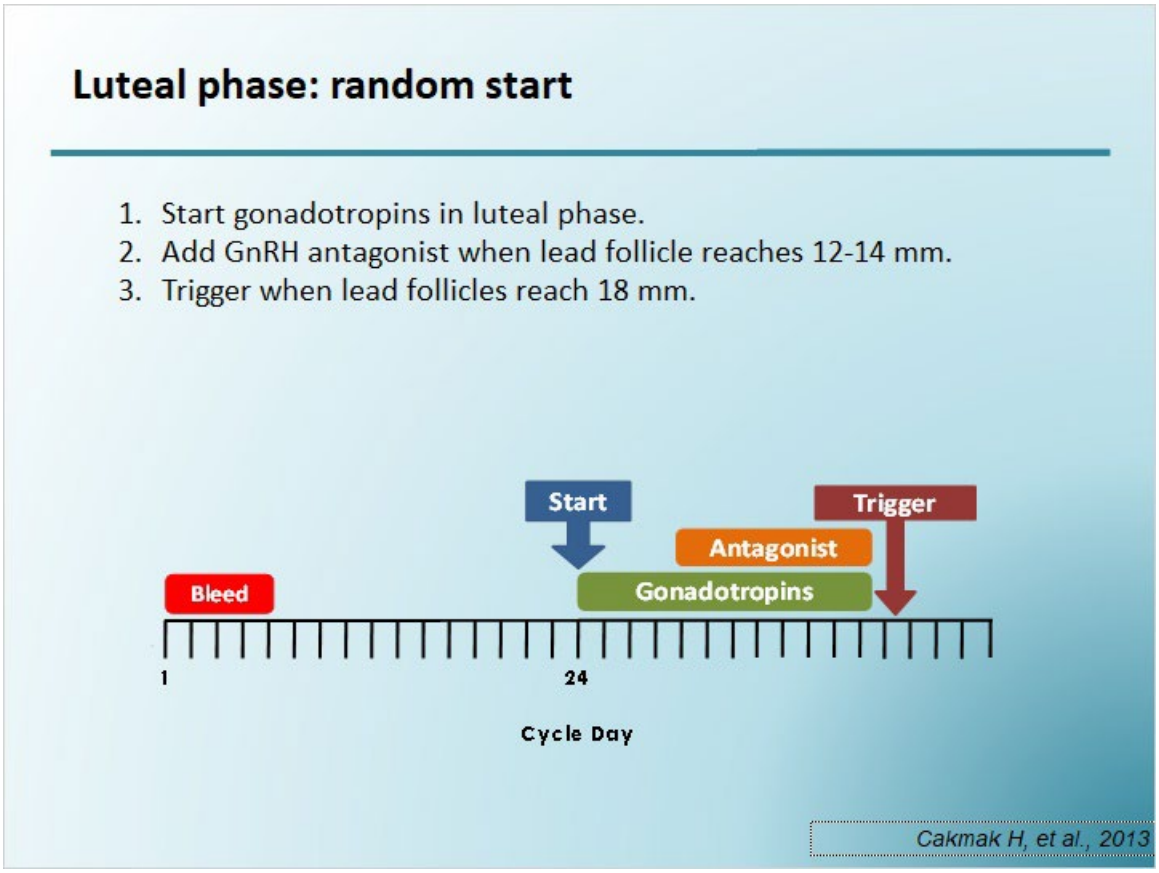
1.12 Luteolysis option #2: data



Notes:

This approach as been examined in a study of 40 women with cancer, 28 of whom were stimulated in their early follicular phase and 12 of whom underwent luteal phase starts with luteolysis. Women stimulated in their luteal phase tended to be slightly older with slightly fewer numbers of aspirated oocytes, though the percentage of viable metaphase II oocytes was comparable between the groups. It is worth nothing that the study was small and data were unadjusted for any confounding factors.

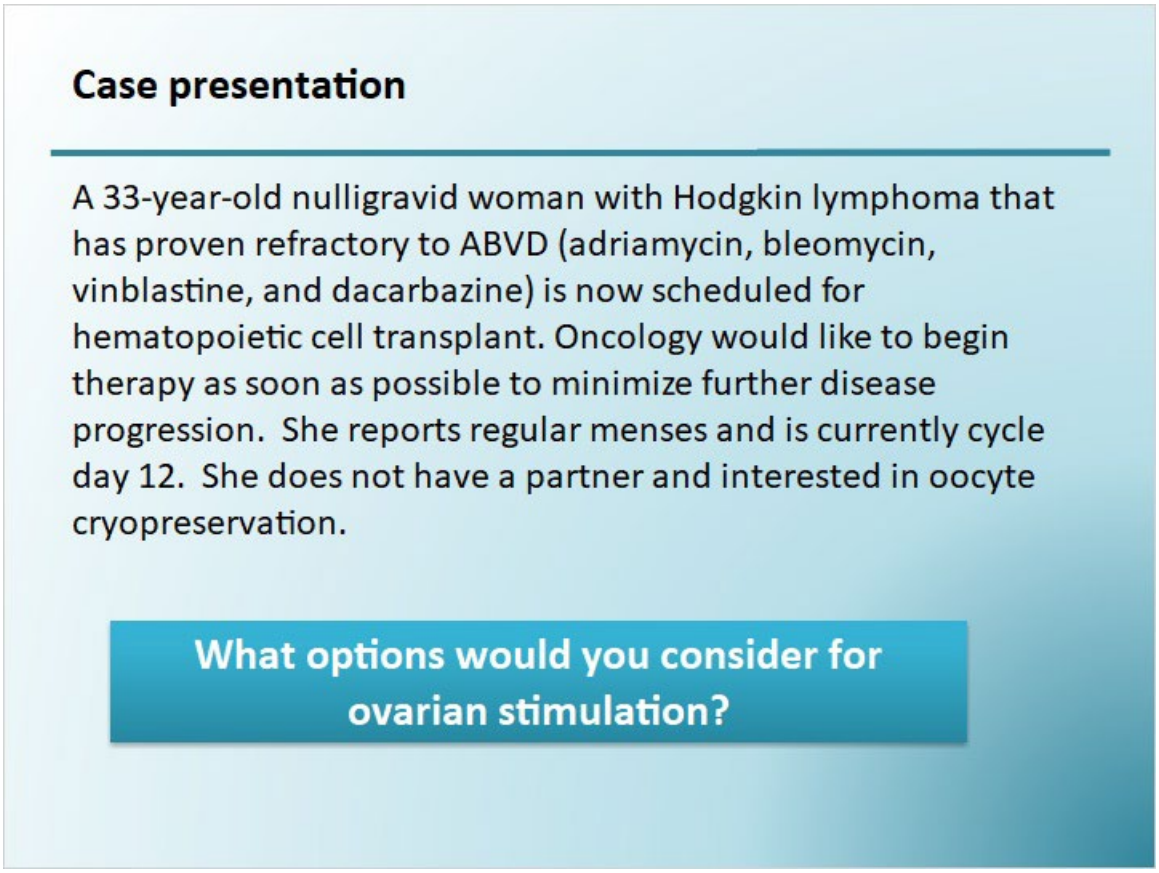
1.13 Luteal phase: random start



Notes:

A third, more recently described approach to luteal phase stimulation is a “random start” where ovarian stimulation is initiated in a similar fashion regardless of the menstrual phase. Here, a standard GnRH antagonist protocol is initiated in the luteal phase. As previously described, GnRH antagonists are added when the lead follicle reaches 12 to 14 mm in diameter and ovulation is triggered when the lead follicles exceed 18 mm. Outcome data from this type of stimulation will be discussed in an upcoming slide.

1.14 Case presentation

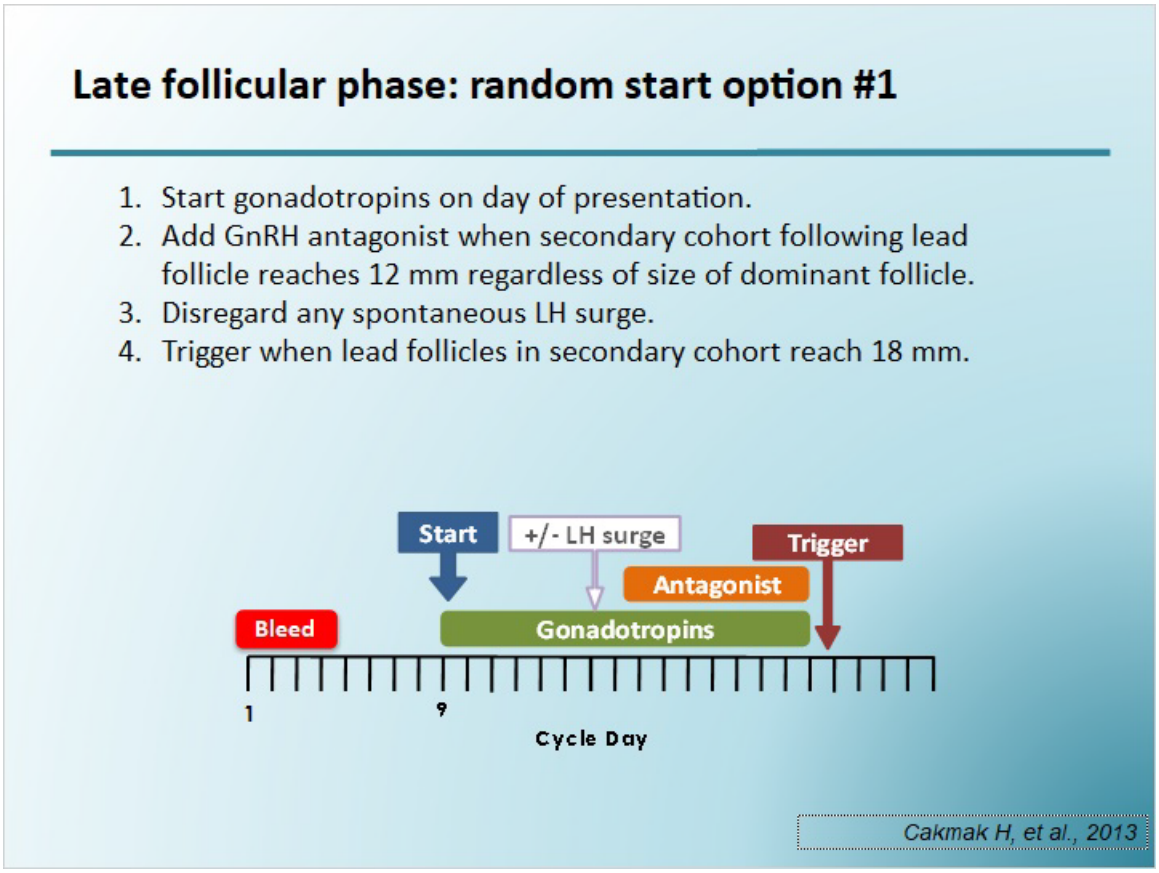


Notes:

The third case is that of a 23-year-old nulligravid woman with recurrent Hodgkin lymphoma who is scheduled to undergo hematopoietic stem cell transplant. She has previously undergone chemotherapy with ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine), a regimen thought to have a comparably low risk of gonadotoxicity. She is single and interested in oocyte cryopreservation prior to immunosuppression. Her oncologist would like oocyte retrieval to occur as quickly as possible given the urgent need to begin therapy. She has regular menses and presents for evaluation on cycle day 12.

What options would you consider for ovarian stimulation?

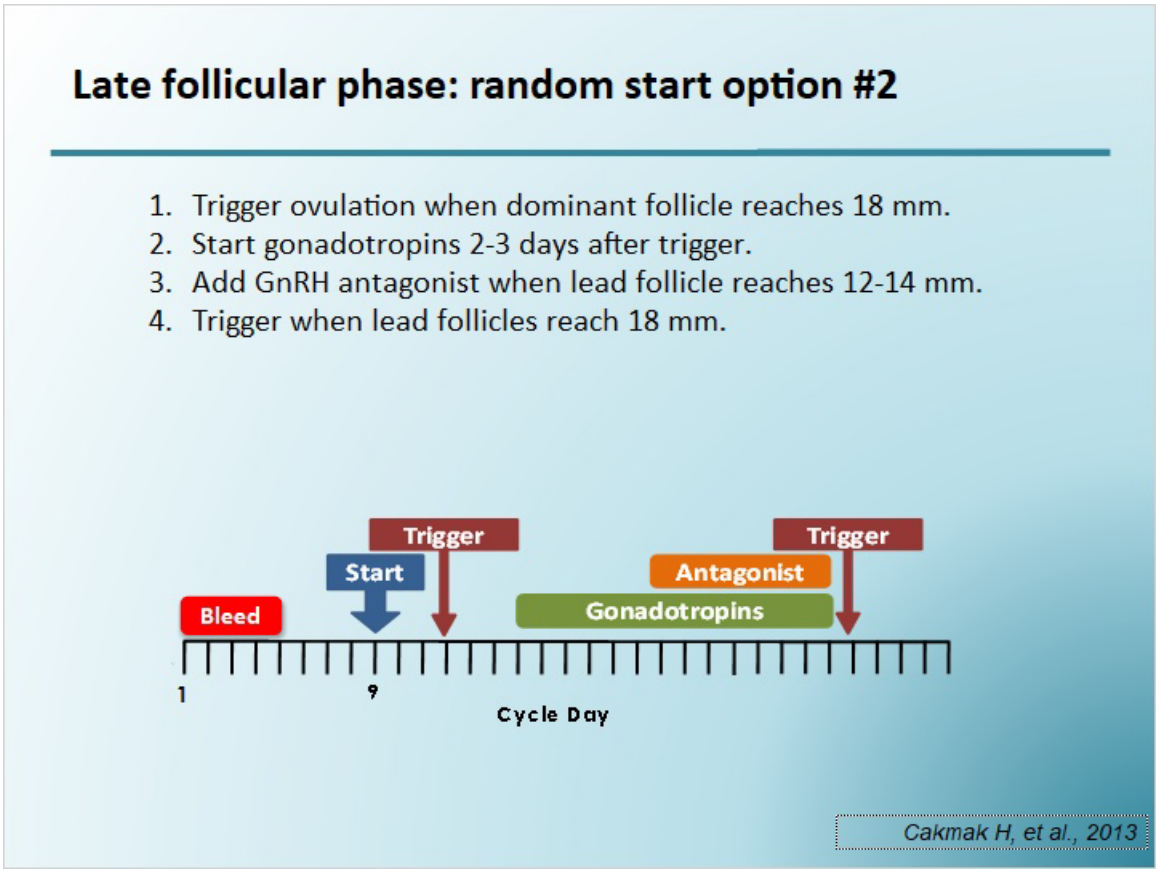
1.15 Late follicular phase: random start option #1



Notes:

Two protocols have been described to specifically address ovarian stimulation for fertility preservation patients who present in their late follicular phase (cycle days 7-14), both of which adopt a “random start” approach. The first, pictured here, is again similar to a standard GnRH antagonist protocol except that gonadotropin therapy is initiated in the late follicular phase. As a dominant follicle would have likely been recruited at the time of cycle start, a spontaneous LH surge is possible during stimulation. Ovulation is therefore triggered only when the size of the secondary follicular cohort exceeds 18 mm.

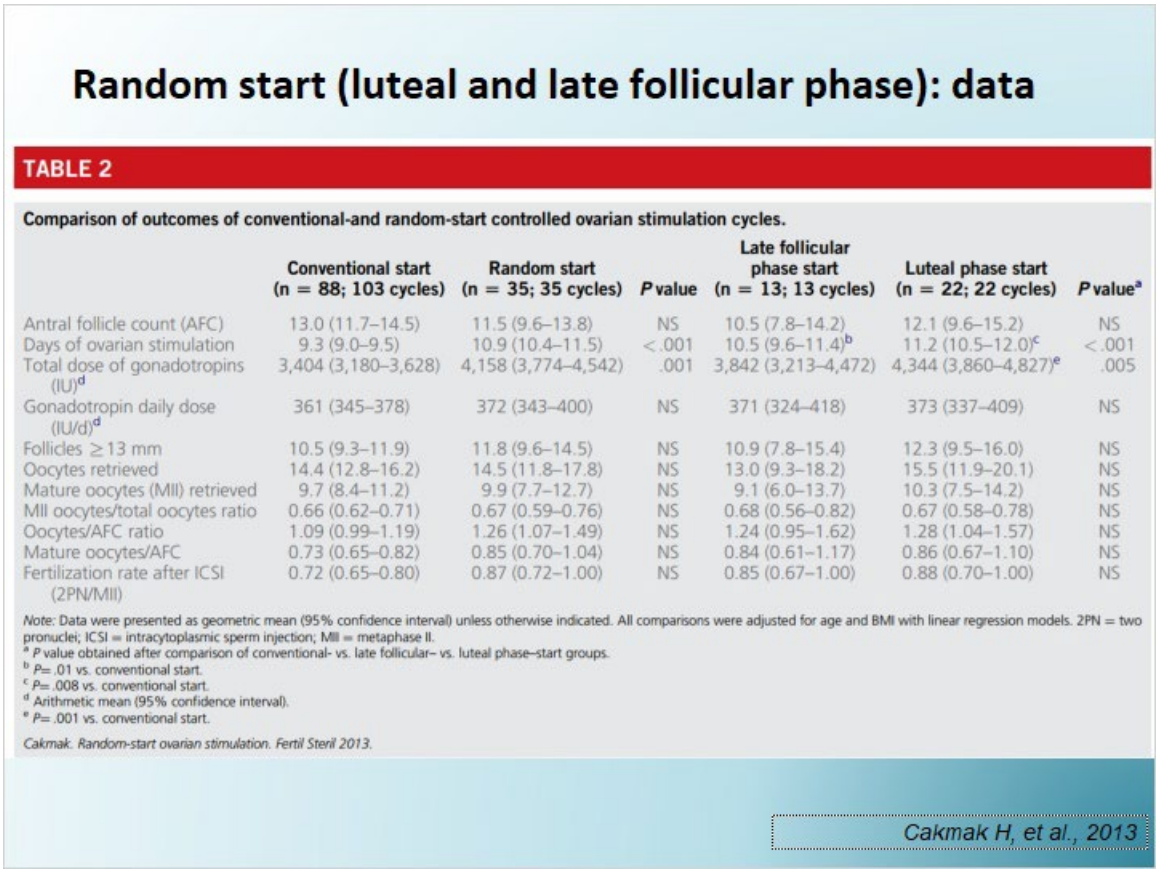
1.16 Late follicular phase: random start option #2



Notes:

The second protocol for late follicular phase stimulation involves inducing ovulation with hCG or a GnRH agonist when the previously recruited dominant follicle reaches 18 mm. Ovarian stimulation is started via a standard GnRH antagonist protocol 2 to 3 days into the luteal phase.

1.17 Random start (luteal and late follicular phase): data



Random start (luteal and late follicular phase): data

TABLE 2

Comparison of outcomes of conventional-and random-start controlled ovarian stimulation cycles.

	Conventional start (n = 88; 103 cycles)	Random start (n = 35; 35 cycles)	*P* value	Late follicular phase start (n = 13; 13 cycles)	Luteal phase start (n = 22; 22 cycles)	*P* value[a]
Antral follicle count (AFC)	13.0 (11.7–14.5)	11.5 (9.6–13.8)	NS	10.5 (7.8–14.2)	12.1 (9.6–15.2)	NS
Days of ovarian stimulation	9.3 (9.0–9.5)	10.9 (10.4–11.5)	<.001	10.5 (9.6–11.4)[b]	11.2 (10.5–12.0)[c]	<.001
Total dose of gonadotropins (IU)[d]	3,404 (3,180–3,628)	4,158 (3,774–4,542)	.001	3,842 (3,213–4,472)	4,344 (3,860–4,827)[e]	.005
Gonadotropin daily dose (IU/d)[d]	361 (345–378)	372 (343–400)	NS	371 (324–418)	373 (337–409)	NS
Follicles ≥13 mm	10.5 (9.3–11.9)	11.8 (9.6–14.5)	NS	10.9 (7.8–15.4)	12.3 (9.5–16.0)	NS
Oocytes retrieved	14.4 (12.8–16.2)	14.5 (11.8–17.8)	NS	13.0 (9.3–18.2)	15.5 (11.9–20.1)	NS
Mature oocytes (MII) retrieved	9.7 (8.4–11.2)	9.9 (7.7–12.7)	NS	9.1 (6.0–13.7)	10.3 (7.5–14.2)	NS
MII oocytes/total oocytes ratio	0.66 (0.62–0.71)	0.67 (0.59–0.76)	NS	0.68 (0.56–0.82)	0.67 (0.58–0.78)	NS
Oocytes/AFC ratio	1.09 (0.99–1.19)	1.26 (1.07–1.49)	NS	1.24 (0.95–1.62)	1.28 (1.04–1.57)	NS
Mature oocytes/AFC	0.73 (0.65–0.82)	0.85 (0.70–1.04)	NS	0.84 (0.61–1.17)	0.86 (0.67–1.10)	NS
Fertilization rate after ICSI (2PN/MII)	0.72 (0.65–0.80)	0.87 (0.72–1.00)	NS	0.85 (0.67–1.00)	0.88 (0.70–1.00)	NS

Note: Data were presented as geometric mean (95% confidence interval) unless otherwise indicated. All comparisons were adjusted for age and BMI with linear regression models. 2PN = two pronuclei; ICSI = intracytoplasmic sperm injection; MII = metaphase II.

[a] *P* value obtained after comparison of conventional- vs. late follicular– vs. luteal phase–start groups.

[b] *P*= .01 vs. conventional start.

[c] *P*= .008 vs. conventional start.

[d] Arithmetic mean (95% confidence interval).

[e] *P*= .001 vs. conventional start.

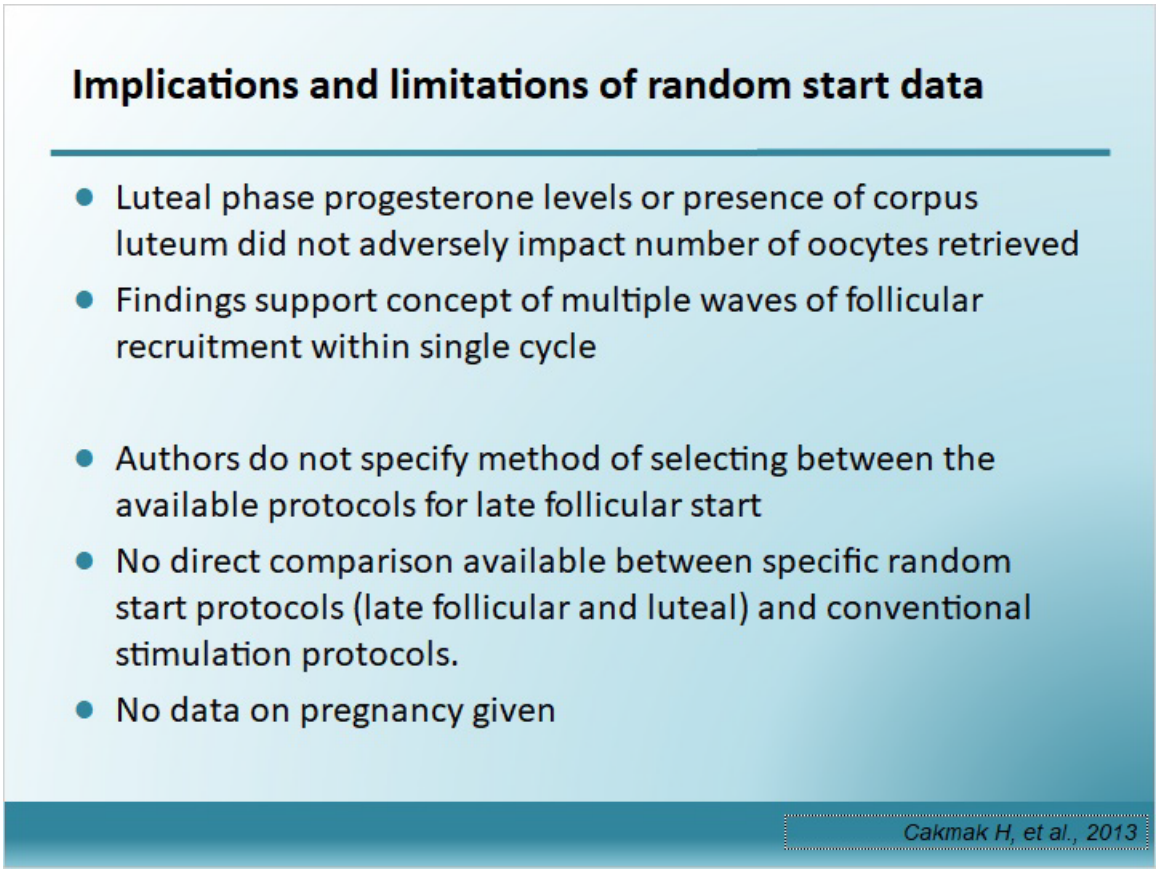
Cakmak. Random-start ovarian stimulation. Fertil Steril 2013.

Cakmak H, et al., 2013

Notes:

A comparison of 88 patients who initiated a conventional GnRH antagonist-based stimulation in their early follicular phase to 35 patients who underwent random start stimulation in either the late follicular or luteal phases showed longer stimulations and higher total gonadotropin doses in random-start as compared with conventional-start cycles. Numbers of total or mature oocytes did not differ between the groups. Late follicular phase random starts stimulations were shorter than those initiated in the luteal phase, but with comparable oocyte parameters.

1.18 Implications and limitations of random start data

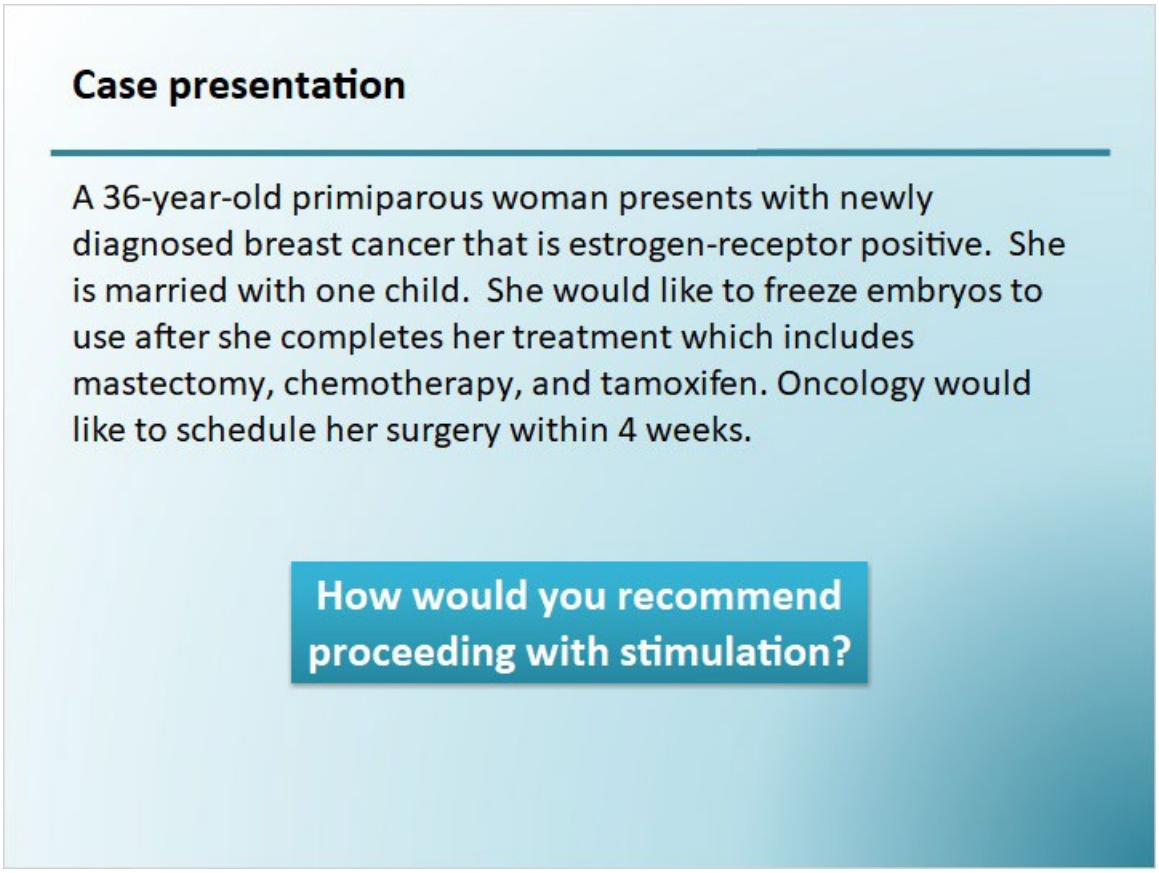


Notes:

It is interesting that the elevated progesterone levels and presence of corpus luteum that characterize the luteal phase did not have a negative impact on the number of oocytes retrieved. This finding supports the idea that multiple waves of follicular recruitment may take place within a single cycle.

The study authors do not specify their methodology of selecting between the two proposed protocols for random start stimulations in the late follicular phase. Moreover, no direct comparisons are available between individual random start protocols (late follicular and luteal phase) and conventional stimulation. Finally, no data are yet available on pregnancies originating from these embryos.

1.19 Case presentation

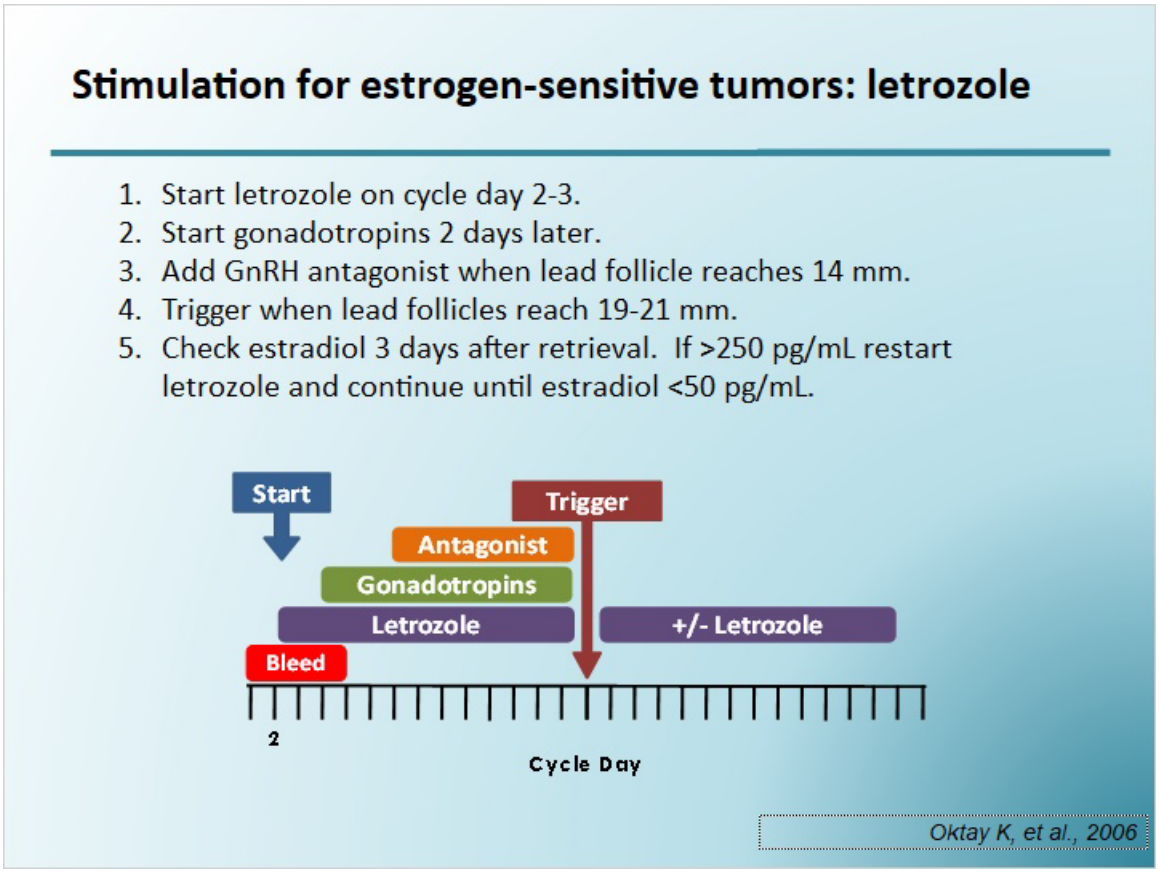


Notes:

The final case is that of a 36-year-old woman, gravida 1, para 1, now with newly diagnosed estrogen-receptor-positive breast cancer. She is planning to undergo surgery, chemotherapy, and tamoxifen but would like to freeze embryos for future use once she has completed her cancer therapy. Oncology is willing to delay her surgery for up to one month to allow time for this process.

How would you recommend proceeding with stimulation?

1.20 Stimulation for estrogen-sensitive tumors: letrozole



Notes:

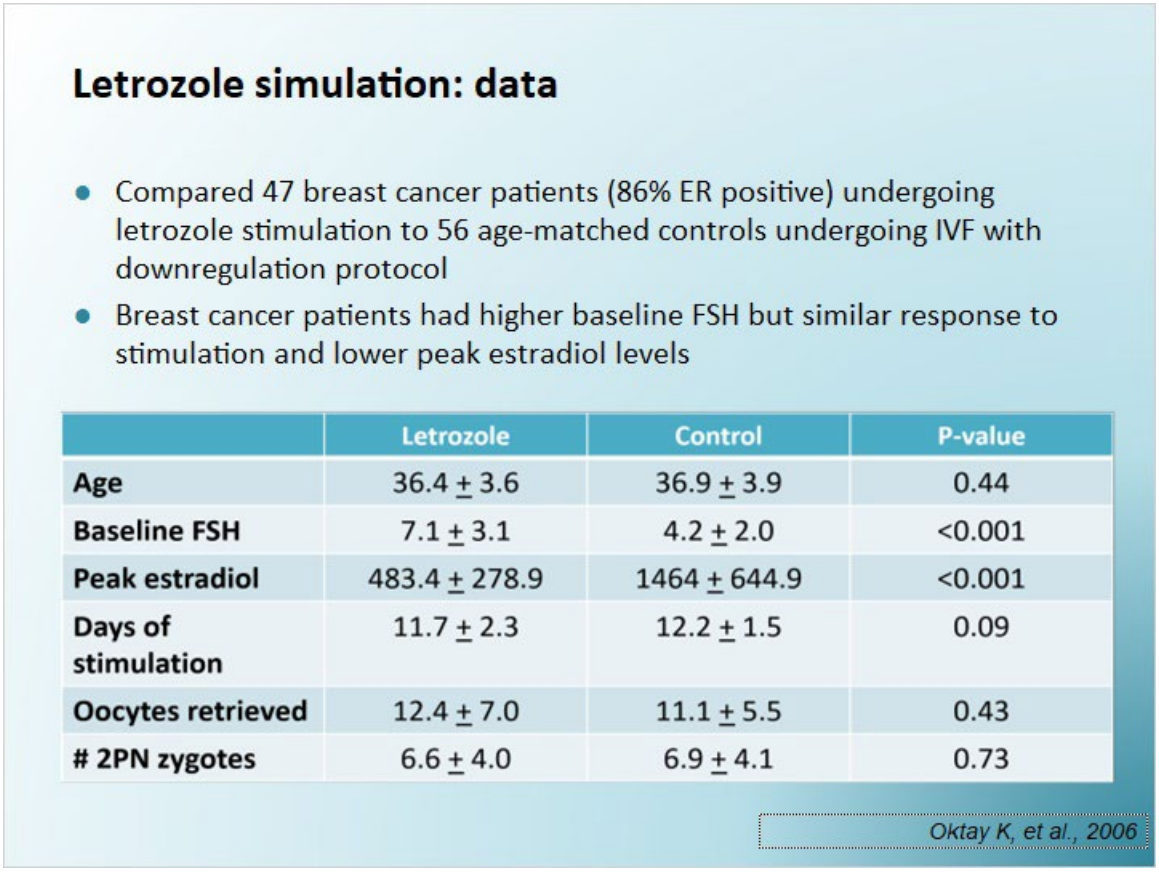
Women with estrogen-sensitive tumors such as breast or endometrial cancers may wish to avoid the supraphysiologic estradiol levels that accompany controlled ovarian stimulation using traditional protocols. An alternative is to utilize the aromatase inhibitor letrozole in conjunction with gonadotropins to minimize circulating estradiol levels during stimulation. In this protocol, letrozole is begun on day 2-3 of a spontaneous or induced cycle. Gonadotropins are added after 2 days of letrozole exposure, though many practitioners may start letrozole and gonadotropins concurrently in order to expedite stimulation. A GnRH antagonist is given when the lead follicle reaches 14 mm. Ovulation is triggered when the lead follicles reach 19-21 mm to allow for a larger cohort of mature oocytes. Letrozole may be discontinued on the day of trigger. If serum estradiol remains elevated after oocyte retrieval, letrozole is restarted.

In most cases, women with estrogen-sensitive tumors are not under significant time pressure to undergo treatment, thus enabling an early follicular phase start as described above. If, however, an individual woman has a shorter timeline, letrozole can be utilized in a similar fashion with any of the luteal or late follicular phase starts previously

described.

Many practitioners will schedule ovarian stimulation in breast cancer patients after surgery but before any planned chemotherapy. This approach may minimize potential for tumor growth as surgery has removed the bulk of the disease, although this benefit remains theoretical.

1.21 Letrozole simulation: data

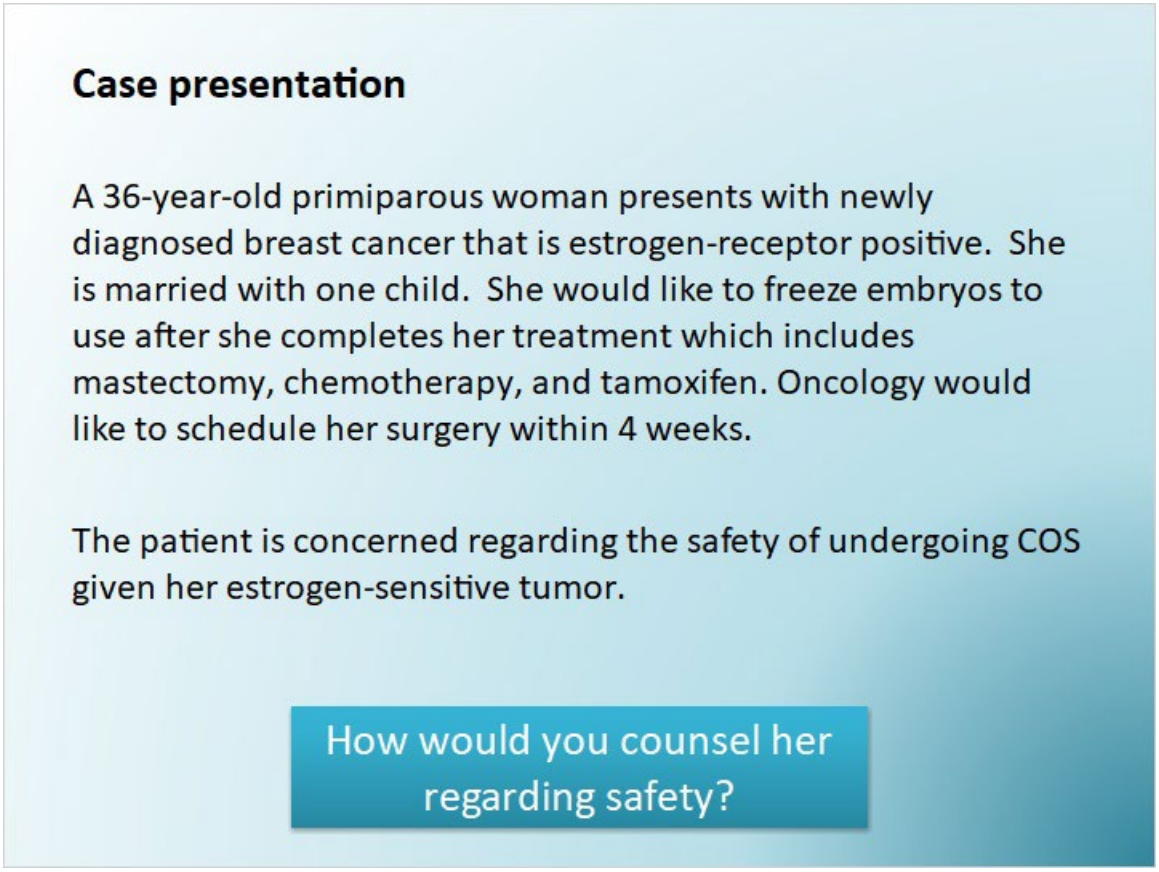


	Letrozole	Control	P-value
Age	36.4 ± 3.6	36.9 ± 3.9	0.44
Baseline FSH	7.1 ± 3.1	4.2 ± 2.0	<0.001
Peak estradiol	483.4 ± 278.9	1464 ± 644.9	<0.001
Days of stimulation	11.7 ± 2.3	12.2 ± 1.5	0.09
Oocytes retrieved	12.4 ± 7.0	11.1 ± 5.5	0.43
# 2PN zygotes	6.6 ± 4.0	6.9 ± 4.1	0.73

Notes:

The efficacy of a letrozole-based stimulation has been evaluated in a study comparing 47 patients with breast cancer with 56 age-matched controls with tubal factor infertility undergoing IVF with a standard downregulation protocol. The higher mean baseline FSH levels among breast cancer patients may be indicative of the impact of malignancy and chronic disease on ovarian reserve, though this finding is not consistent in the literature. Peak serum estradiol levels were significantly lower after letrozole stimulation, and outcome parameters including numbers of oocytes and 2PN zygotes were similar to a standard downregulation stimulation.

1.22 Case presentation

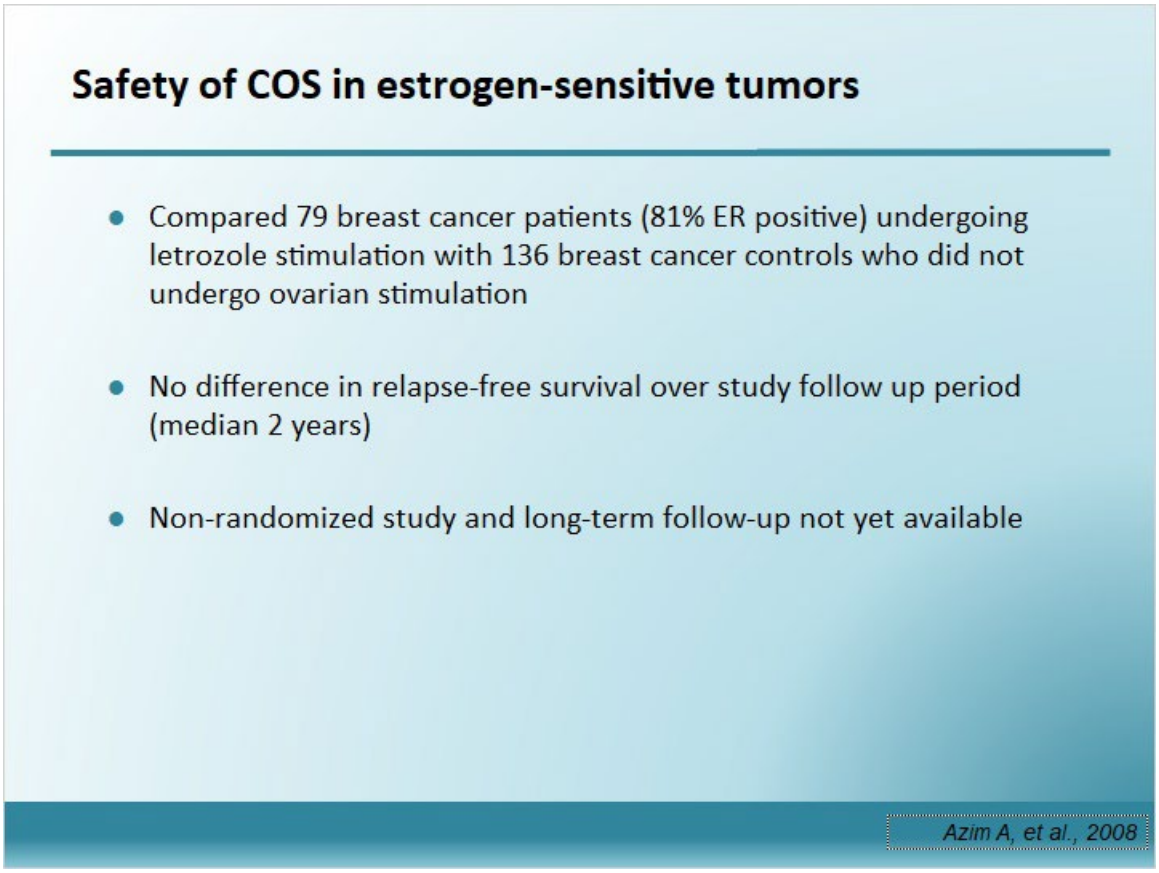


Notes:

The patient appreciates the recommendation for a letrozole-based stimulation to minimize circulating estradiol levels, but is still concerned regarding its safety with respect to cancer recurrence.

How would you counsel her regarding the safety of this protocol?

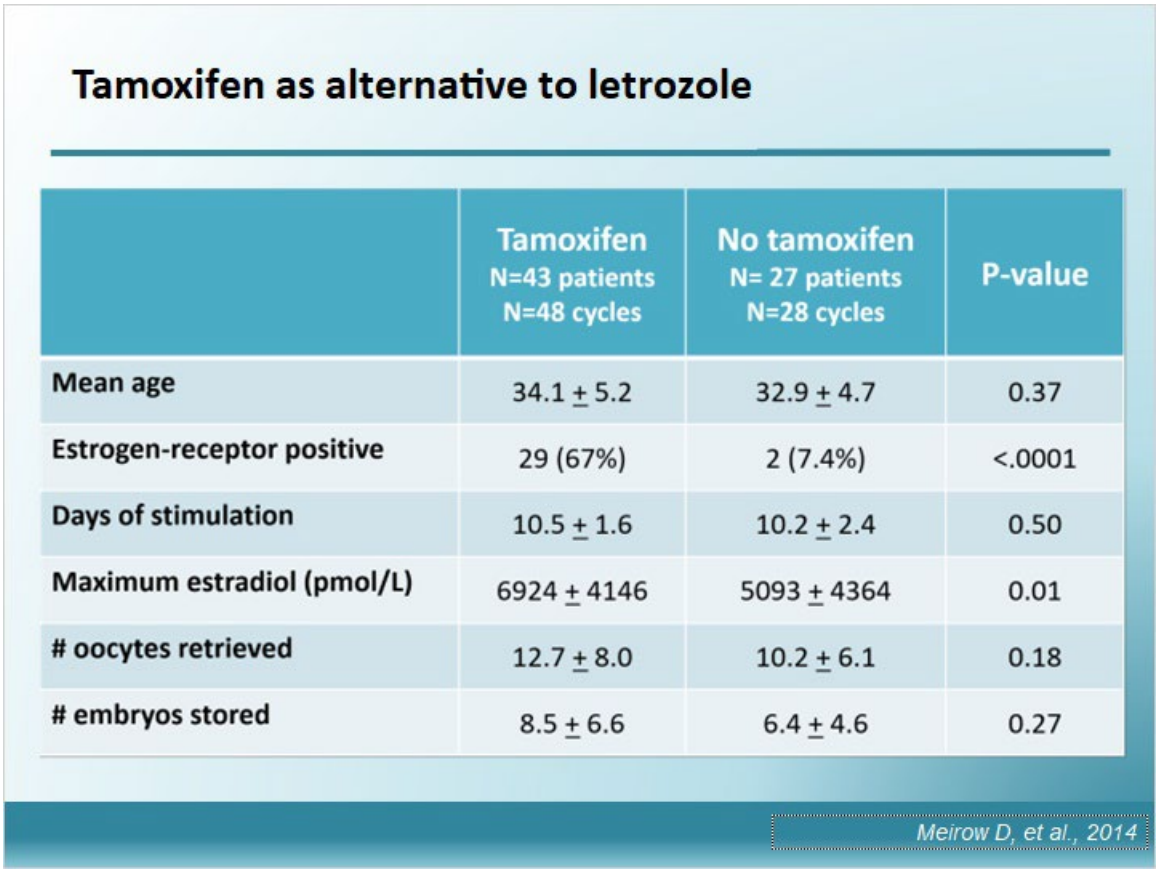
1.23 Safety of COS in estrogen-sensitive tumors



Notes:

The safety of letrozole-based stimulation protocols has been examined in a study comparing 79 breast cancer patients, 81% of whom had an estrogen-receptor-positive cancer, with 136 control patients with breast cancer who did not undergo ovarian stimulation. The median follow-up time of the study was 2 years, ranging from 23 months in the letrozole group to 33 months in the control group. During this time period, there were 3 (4%) recurrences in the letrozole group and 11 (8%) in the control group. There was no significant difference in relapse-free survival between the groups. This study was not randomized so selection bias may be present, but the experimental and control groups were similar with respect to age and prognostic markers for cancer recurrence. Long-term follow up data are not yet available though recurrence risk is generally thought to be highest during the first 2 years after treatment.

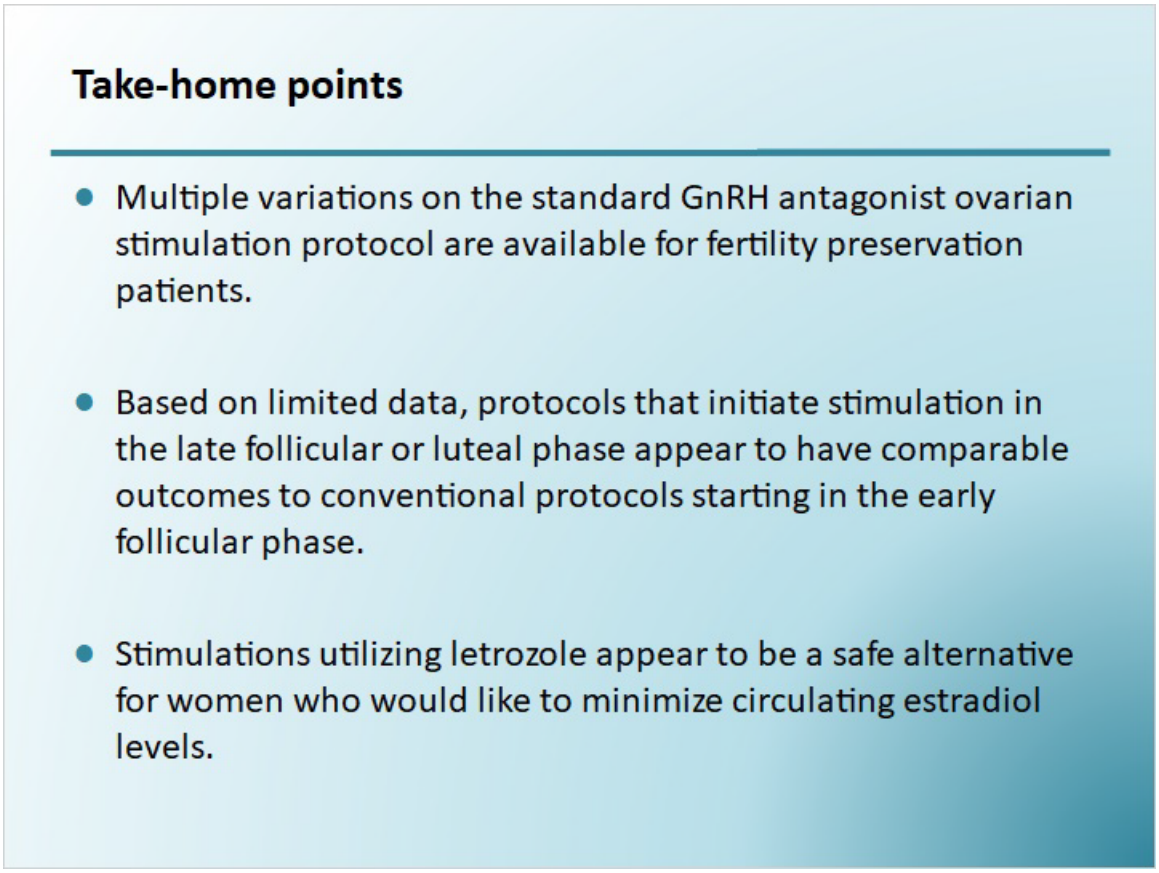
1.24 Tamoxifen as alternative to letrozole



Notes:

Tamoxifen has been explored as an alternative to letrozole for controlled ovarian hyperstimulation in estrogen-receptor-positive breast cancer patients due to its established use for chemoprevention in this population. Mean numbers of oocytes retrieved and embryos frozen were comparable between 43 breast cancer patients treated with tamoxifen during ovarian stimulation and 27 patients who did not receive the drug. Mean estradiol levels were notably higher in the tamoxifen group, though 10-year cancer recurrence risk was unchanged. As the study was not randomized, women receiving tamoxifen were significantly more likely to have a hormone-receptor-positive cancer, a difference that may confound the association between tamoxifen exposure and long term cancer outcome.

1.25 Take-home points



Notes:

In summary, multiple variations on the standard GnRH antagonist ovarian stimulation protocol are available for fertility preservation patients. The reproductive endocrinologist should be familiar with the principles that underlie these variations in order to select the most appropriate means of controlled ovarian stimulation for a given patient. Existing data suggest that protocols that initiate stimulation in the late follicular or luteal phase have comparable outcomes to conventional protocols starting in the early follicular phase. Stimulations utilizing letrozole appear to be a safe alternative for women who would like to minimize circulating estradiol levels due to estrogen-sensitive neoplasms, though no data have specifically examined embryo quality using this approach. Additional studies evaluating the comparative efficacy of individual protocols in specific populations continue to be warranted.

1.26 Thank you!

Notes:

Thank you for your participation. We hope you enjoyed the course.