UNCONVENTIONAL OVARIAN STIMULATION PROTOCOLS: INDICATIONS EXTEND BEYOND EMERGENCY FERTILITY PRESERVATION

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• Nothing to disclose
• No conflict of interest
Unconventional stimulation protocols in IVF

- Oocyte/embryo freezing before cancer therapy
- Elective oocyte freezing
- Poor-responders
- General IVF population
Unconventional stimulation protocols in IVF

- Oocyte/embryo freezing before cancer therapy
- Elective oocyte freezing
- Poor-responders
- General IVF population

Random start protocols

- Random start
- Delayed start
- CC or letrozole

- Progesterone-priming OS (PPOS)
Ovarian tissue cryo
Oocyte/embryo freezing

Oktem et al Oncologist 2018
For many solid tumors including breast cancer

Cancer diagnosis

- Advanced stage
- Aggressive tumors

Surgery

CONVENTIONAL IVF
4-6 weeks

CHEMOTHERAPY
RADIATION

NEOADJUVANT
CHEMOTHERAPY
RADIATION

URGENT IVF

Days
Controlled ovarian stimulation (COS) for embryo or mature oocyte cryopreservation, which is the only technique endorsed by the American Society of Reproductive Medicine, is the most preferred method for fertility preservation in patients with cancer because of its higher success rates compared with other more experimental technologies.
• Conventionally, ovarian stimulation for oocyte/embryo cryopreservation is initiated at the beginning of the follicular phase with the idea that this optimizes clinical outcomes.

• However, this methodology may require 2 – 6 weeks depending on the women’s menstrual cycle phase at the time of presentation.

• As a result, there remains the possibility of a significant delay of cancer treatment and the potential for increased psychological stress for the patient and oncologist that may lead to patients forgoing fertility preservation.
GnRH Antagonist Cycles vs Long GnRH Agonist Cycles

Long Agonist Protocol

GnRH Agonist

FSH

Antagonist Protocol

GnRH Antagonist

Flare-up

Pituitary downregulation

Direct Gonadotropin suppression

LH

Time
As there is often an urgent need to start cancer treatment, new protocols to facilitate the start of the ovarian stimulation and oocyte/embryo cryopreservation process have been proposed (RANDOM START).
Random-start controlled ovarian hyperstimulation for emergency fertility preservation in letrozole cycles.

Sönmezêr M¹, Türkçüoğlu İ, Coşkun U, Oktay K.

Author information

Abstract

OBJECTIVE: To report an emergency approach of random-start controlled ovarian hyperstimulation (COH) in the late follicular or luteal phase of the menstrual cycle for embryo cryopreservation in patients with cancer.

DESIGN: Case series.

SETTING: Academic tertiary referral centers.

PATIENT(S): Three patients with a diagnosis of breast cancer requiring emergency fertility preservation in the late follicular or luteal phase of the menstrual cycle.

INTERVENTION(S): After baseline pelvic ultrasound and hormonal evaluation, random-start COH was commenced immediately on menstrual cycle days 11, 14, or 17 with use of letrozole 2.5 mg/d and recombinant FSH 150 to 300 IU/d. Gonadotropin-releasing hormone antagonist was administered to prevent ovulation in all cases. Ovulation was triggered with either 250 µg of recombinant hCG or 10,000 IU of urinary hCG.

MAIN OUTCOME MEASURE(S): Number of oocytes harvested, maturity and fertilization rates, number of embryos frozen.

RESULT(S): Nine to 17 oocytes were harvested, resulting in the freezing of seven to 10 embryos with the mean maturity and fertilization rates of 58.8% to 77.7% and 69.2% to 87.5%, respectively.

CONCLUSION(S): In an emergent setting, ovarian stimulation can be started at a random cycle date for the purpose of fertility preservation without compromising fertilization rates in letrozole cycles.

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[Indexed for MEDLINE]
Induction of luteolysis with a GnRH antagonist (single dose 3mg or 0.25mg for 3 days)

Serum P declines and menses ensue.

As a result, ovarian stimulation would be initiated earlier than awaiting spontaneous menses.

GnRH antagonist would be restarted in a standard fashion to prevent premature LH surge during ovarian stimulation.

Although only few studies have been reported, the evidence suggests that a synchronized cohort of follicles can develop with normal fertilization rates and embryo quality.

Oktem O. Int J Gynecol Cancer 2015;25:628-629
• A 31 year old single woman diagnosed with a colorectal tumor.
• She was on day 14 of the cycle and was ovulating from the right ovary as documented by her LH level of 36.1 mIU/mL and progesterone level of 6.1 ng/mL.
• Ultrasound showed a 22x18 mm collapsing follicle with irregular borders and free fluid in the cul de sac as other findings of ovulation. E₂ was 213 pg/mL and FSH was 8.2 mIU/mL.
• 12 mature oocytes retrieved and vitrified.
• If the patient with cancer presents in the late follicular phase, (E) ovulation can be induced with hCG or GnRH agonist when the dominant follicle reaches 18mm in diameter and ovarian stimulation is started in 2–3 days in luteal phase.

• If the patient with cancer presents in the luteal phase, (F) ovarian stimulation can be started in the absence of GnRH antagonist and GnRH antagonist administration is initiated later in the cycle, when the follicle cohort reached 12mm to prevent premature secondary LH surge.

Oktem O. Int J Gynecol Cancer 2015;25:628-629
In contrast to previous belief, the presence of corpus luteum or luteal phase progesterone levels did not adversely affect synchronized follicular development, number of mature oocytes retrieved, and/or fertilization rates.

Because spontaneous corpus luteum regression occurs possibly due to suppressive effect of rising estradiol levels on endogenous LH secretion during COS, corpus luteum regression with GnRH antagonist was not necessary to start COS.

Recombinant FSH should be used to avoid endogenous LH activity that may prevent luteolysis.

The length of the cycle and daily gonadotropin dose were not affected by the serum progesterone level or whether COS was started in the early or mid-luteal phase.

In addition, the ovary with corpus luteum had similar number of dominant follicles (13 mm) compared with the patient’s other ovary on the day of trigger shot.

Ovarian stimulation without GnRH antagonist was started if the follicle cohort following the lead follicle was smaller than 12 mm and stayed smaller than 12 mm before a spontaneous LH surge.

After the LH surge, GnRH antagonist was started when the secondary follicle cohort reached 12 mm to prevent premature secondary LH surge.

If the follicle cohort following the lead follicle reached 12 mm before the spontaneous LH surge, pituitary suppression with GnRH antagonist was initiated and continued until triggering final oocyte maturation.
Table 1. Comparison between conventional, late follicular and luteal start IVF cycles; median (interquartile range)

<table>
<thead>
<tr>
<th></th>
<th>Conventional start (n = 136)</th>
<th>Late follicular start (n = 32)</th>
<th>Luteal start (n = 44)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicles ≥ 13 mm</td>
<td>12.5 (6.5–17)</td>
<td>14.0 (9.0–19.75)</td>
<td>13.0 (8.25–16.75)</td>
<td>NS</td>
</tr>
<tr>
<td>Mature oocytes (MII) retrieved</td>
<td>11 (6.5–16)</td>
<td>12.0 (7.0–16.75)</td>
<td>10.0 (5.25–15)</td>
<td>NS</td>
</tr>
<tr>
<td>MII oocyte/total oocyte ratio</td>
<td>0.71 (0.60–0.82)</td>
<td>0.75 (0.63–0.83)</td>
<td>0.72 (0.60–0.84)</td>
<td>NS</td>
</tr>
<tr>
<td>Mature oocyte/AFC ratio</td>
<td>0.83 (0.46–1.12)</td>
<td>0.91 (0.64–1.27)</td>
<td>0.86 (0.58–1.17)</td>
<td>NS</td>
</tr>
<tr>
<td>Fertilization rate (2PN/MII)</td>
<td>0.79 (0.67–0.85)</td>
<td>0.86 (0.78–1.00)</td>
<td>0.87 (0.76–1.00)</td>
<td>NS</td>
</tr>
<tr>
<td>High-quality day 3 embryos/2PN ratio</td>
<td>0.92 (0.76–1.00)</td>
<td>0.91 (0.81–1.00)</td>
<td>0.88 (0.83–1.00)</td>
<td>NS</td>
</tr>
</tbody>
</table>

AFC, antral follicle count; NS, not significant.
The number of total and MII oocytes derived from random-start ovarian stimulation protocols initiated during any phase of the menstrual cycle are similar to conventional CD 2/3 ovarian stimulation start protocols. Thus, random-start ovarian stimulation can be a valuable alternative to conventional start in women desiring elective cryopreservation of oocytes.

Perera et al RBM online 2017

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**Table 2 - Comparison of controlled ovarian stimulation outcomes stratified by type (n = 1302).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 859)</th>
<th>Early follicular (n = 342)</th>
<th>Late follicular (n = 42)</th>
<th>Luteal (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GnRH-agonist based</td>
<td>93 (10.8)</td>
<td>55 (16.1)</td>
<td>6 (14.3)</td>
<td>9 (15.3)</td>
</tr>
<tr>
<td>GnRH-antagonist based</td>
<td>766 (89.2)</td>
<td>287 (83.9)</td>
<td>36 (85.7)</td>
<td>50 (84.7)</td>
</tr>
<tr>
<td>Total stimulation days*</td>
<td>9.5 (8-11)</td>
<td>9.5 (8.5-12)</td>
<td>11.5 (7.5-13.5)</td>
<td>11 (8-12)</td>
</tr>
<tr>
<td>Total gonadotrophin dose (IU)*</td>
<td>3155 (2100-4500)</td>
<td>3280 (2180-4700)</td>
<td>4665.5 (3300-5975)</td>
<td>4345 (3100-5650)</td>
</tr>
<tr>
<td>Gonadotrophin dose/day (IU/day)*</td>
<td>332.1</td>
<td>345.3</td>
<td>405.7</td>
<td>395.0</td>
</tr>
<tr>
<td>Trigger type n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.m. HCG</td>
<td>197 (22.9)</td>
<td>94 (27.5)</td>
<td>9 (21.4)</td>
<td>15 (25.4)</td>
</tr>
<tr>
<td>subcutaneous HCG</td>
<td>449 (52.3)</td>
<td>192 (56.1)</td>
<td>20 (47.6)</td>
<td>29 (49.2)</td>
</tr>
<tr>
<td>Dual leuprolide and HCG</td>
<td>152 (17.7)</td>
<td>37 (10.8)</td>
<td>8 (19.1)</td>
<td>11 (18.6)</td>
</tr>
<tr>
<td>Pure leuprolide</td>
<td>61 (7.1)</td>
<td>19 (5.6)</td>
<td>5 (11.9)</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>Oestradiol on day of trigger (pg/ml)</td>
<td>1796 (1189-2540)</td>
<td>1781 (1045.5-2583.5)</td>
<td>1804 (1058.5-2661)</td>
<td>1789 (1052-2504)</td>
</tr>
<tr>
<td>Oestradiol after day of trigger (pg/ml)</td>
<td>2509 (1619.5-3372.5)</td>
<td>2495.5 (1442.5-3298.5)</td>
<td>2488 (1674-3174.5)</td>
<td>2465 (1309-3174.5)</td>
</tr>
<tr>
<td>Cancellation rate n (%)</td>
<td>31 (3.6)</td>
<td>12 (3.5)</td>
<td>3 (7.1)</td>
<td>2 (3.4)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) and median (interquartile range).

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**Table 3 - Yield of total and metaphase II oocytes stratified by controlled ovarian stimulation type (n = 1302).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 859)</th>
<th>Early follicular (n = 342)</th>
<th>Late follicular (n = 42)</th>
<th>Luteal (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total oocytes retrieved</td>
<td>13.1 (±2.3)</td>
<td>12.7 (±2.7)</td>
<td>13.0 (±3.1)</td>
<td>13.2 (±2.9)</td>
</tr>
<tr>
<td>MII oocytes retrieved</td>
<td>11.0 (±3.1)</td>
<td>10.8 (±2.7)</td>
<td>11.1 (±3.0)</td>
<td>10.9 (±3.2)</td>
</tr>
<tr>
<td>MII oocytes (%)</td>
<td>84.0</td>
<td>85.0</td>
<td>85.4</td>
<td>82.6</td>
</tr>
<tr>
<td>MII oocytes/AFC</td>
<td>0.83</td>
<td>0.84</td>
<td>0.85</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation and n (%).
AFC = antral follicle count; MII = metaphase II.

There were no statistically significant differences between the groups.
Double stimulation

• The evidence indicates that there are more than one follicle recruitment waves during a menstrual cycle.

• It can enable the clinician to obtain more oocytes in a single cycle in two stimulation cycles.

• It shows an ovarian stimulation can be started couple days after egg retrieval to minimize delays.

• Existing antral follicles in the luteal phase enables ovarian stimulation.

Double stimulation

**Figure 1** The protocol of double stimulation during the follicular and luteal phases in patients with poor ovarian response. GnRHa, gonadotrophin-releasing hormone agonist; HMG, human menopausal gonadotrophin; MPA, medroxyprogesterone acetate; qod, every other day.

POOR RESPONDERS

• Bologna criteria
  – maternal age (≥40 years),
  – previous POR (≤3 three oocytes with conventional stimulation) and
  – abnormal ORT (AFC < 5–7 or AMH < 0.5–1.1 ng/ml)
POOR RESPONDERS

- A poor response to COS potentially results in
  - high cancellation rates,
  - a reduced number of oocytes retrieved,
  - a decreased number of embryos available for transfer, and
  - lower pregnancy rate compared with normal responders.

Ferraretti et al Human Reprod 2014
POOR RESPONDERS

• Although many protocols have been proposed to increase ovarian response, there is presently insufficient evidence to support the routine use of any particular intervention either for pituitary down regulation, or ovarian stimulation or adjuvant therapy in the management of poor responders.

POOR RESPONDERS

• Various factors, including decreased ovarian reserve, have been associated with a poor response.
• However, alterations in intra-ovarian factors or gonadotropin receptor regulation could also contribute to suboptimal response.
• Additionally, poor responses may partly result from
  – a shortened follicular phase with limited ability to recruit a sizable cohort, or  
  – differential sensitivity of early antral follicles to FSH.

• The mechanisms underlying the heterogeneity of antral follicle responsiveness to gonadotropins during the early follicular phase remain unclear.
ASYNCHRONOUS FOLLICLE GROWTH

• A possible explanation for this phenomenon involves follicles being at different developmental stages with various FSH receptor levels due to recruitment of these follicles at different time points.

• Another major reason for the variable response to COS is interference due to the actions of endogenous gonadotropins.
Hormone levels: Older and younger reproductive age

Mean daily levels of gonadotropins, sex steroids, and inhibins in older (ages 35 to 46 years; n = 21), shown in red, and younger women (ages 20 to 34 years; n = 23), shown in blue.
FIGURE 8.8 Dynamics of pulsatile luteinizing hormone (LH) secretion in relation to LH (red), FSH (teal), estradiol (green), and progesterone (brown) in the early follicular phase (EFP), midfollicular phase (MFP), and late follicular phase (LFP), during the midcycle surge (MCS) and in the early luteal phase (ELP), midluteal phase (MLP), and late luteal phase (LLP) in normal women (left panel). Menses is indicated by the red rectangle. The dynamic changes in the interpulse interval and amplitude of pulsatile LH secretion in relation to the phases of the menstrual cycle are indicated in the right panel. (Adapted from Hall JE, Martin KA, Taylor AE. Body weight and gonadotropin secretion in normal women and women with reproductive abnormalities. In Hansel W, Bray, GA, Ryan DH. Nutrition and Reproduction [8]:378–393. 1998, Baton Rouge, Louisiana State University Press, Pennington Center Nutrition Series and Hall JE. Neuroendocrine physiology of the early and late menopause. Endocrinol Metab Clin North Am 33:637–659, 2004.)
Ovarian Feedback on the Hypothalamus and Pituitary

• **Negative Feedback**

• *Progesterone*

  Progesterone has a profound effect on gonadotropin secretion that manifests at the hypothalamic level through slowing of pulsatile GnRH secretion.

• This effect requires estrogen priming, likely through upregulation of progesterone receptors in the hypothalamus.
• By this model, neurokinin B (NKB, magenta) stimulates and dynorphin (DYN, red) suppresses kisspeptin release, with kisspeptin (green) stimulating GnRH neuronal firing.

• The onset of a GnRH pulse is triggered by an initial increase of NKB, which stimulates further NKB release (positive feedback loop) and increases kisspeptin output.

• NKB stimulation of KNDy neurons also stimulates DYN release; and after a short period of time, the increase of DYN suppresses kisspeptin (and NKB) release.

• This withdrawal of kisspeptin stimulation terminates the GnRH pulse.
During the last days of the menstrual cycle, paralleling the breakdown of the corpus luteum, FSH concentration increases progressively to preserve antral follicles from atresia and ensure their subsequent growth.

Depending on their inherent sensitivity to FSH, it is possible that some antral follicles are able to respond to the lower amounts of FSH than the others, and therefore to start their development during the late luteal phase and accentuate size discrepancies observed during the first days of the subsequent cycle leading to asynchronous growth with COS.
COS protocols for poor responders are designed to minimize early follicle selection in the luteal phase and optimize the follicular hormonal milieu and antral follicle responsiveness.

One of the reasons behind using GnRH agonist or birth control pills in the late luteal phase is to suppress FSH rise and subsequent premature dominant follicle selection.

• However, for poor responders, down regulation protocol with GnRH agonist or birth control pills before antagonist protocol may cause over-suppression on ovarian function leading to low oocyte yield.

• As a result, incorporating estradiol pretreatment to the GnRH antagonist protocol gained attention to lower endogenous luteal FSH secretion without suppressing the ovarian response.
• In previous studies, estradiol pretreatment was shown to improve follicle synchronization, and eventually resulted in more coordinated follicular development, leading to the recovery of more mature oocytes.

• However, substantial number of patients still suffers from asynchronous follicle growth with this protocol, likely due higher early follicular phase FSH levels compared to down regulated protocols.

“DELAYED START” PROTOCOL WITH GNRH ANTAGONIST IN POOR RESPONDERS

• Delaying start of COS with GnRH antagonist pre-treatment for 7 days after estrogen priming, there will be further suppression of endogenous FSH during the early follicular phase resulting in more FSH responsive follicles, thus improving synchronous follicular development?
Comparison of characteristics and outcomes of conventional and delayed start COS cycles

<table>
<thead>
<tr>
<th></th>
<th>Conventional Start (n=9)</th>
<th>Delayed Start (n=9)</th>
<th>Between-group difference (95% confidence interval)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of ovarian stimulation</td>
<td>11.1 ± 2.0</td>
<td>9.4 ± 1.4</td>
<td>- 1.7 (−3.1, −0.3)</td>
<td>0.024</td>
</tr>
<tr>
<td>Total dose of gonadotropins (IU)</td>
<td>5000 ± 884</td>
<td>4250 ± 641</td>
<td>−750 (−1374, −126)</td>
<td>0.024</td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td>9.5 ± 2.2</td>
<td>10.9 ± 2.5</td>
<td>1.4 (−0.2, 3.1)</td>
<td>0.082</td>
</tr>
<tr>
<td>Follicles ≥ 13 mm</td>
<td>3.9 ± 1.3</td>
<td>6.7 ± 2.2</td>
<td>2.8 (1.3, 4.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Oocytes retrieved</td>
<td>4.3 ± 1.8</td>
<td>6.6 ± 2.6</td>
<td>2.3 (0.13, 4.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mature oocytes (MII) retrieved</td>
<td>2.2 ± 1.1</td>
<td>4.9 ± 2.0</td>
<td>2.7 (1.1, 4.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>MII oocyte / total oocytes ratio</td>
<td>0.53 ± 0.20</td>
<td>0.73 ± 0.10</td>
<td>0.20 (0.01, 0.4)</td>
<td>0.041</td>
</tr>
<tr>
<td>Oocyte / AFC ratio</td>
<td>0.76 ± 0.36</td>
<td>1.13 ± 0.21</td>
<td>0.37 (0.06, 0.68)</td>
<td>0.024</td>
</tr>
<tr>
<td>Mature oocyte / AFC ratio</td>
<td>0.38 ± 0.19</td>
<td>0.86 ± 0.21</td>
<td>0.48 (0.24, 0.72)</td>
<td>0.003</td>
</tr>
<tr>
<td>Fertilization rate after ICSI (2PN/MII)</td>
<td>0.69 ± 0.21</td>
<td>0.86 ± 0.17</td>
<td>0.17 (−0.10, 0.44)</td>
<td>0.17</td>
</tr>
<tr>
<td>Day of transfer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>8 (100%)</td>
<td>6 (67%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>0</td>
<td>3 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embryos Transferred</td>
<td>1.6 ± 1.2</td>
<td>3.4 ± 1.6</td>
<td>1.8 (0.5, 3.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Implantation Rate</td>
<td>0</td>
<td>6.5 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Pregnancy Rate</td>
<td>0</td>
<td>2 (22.2%)</td>
<td></td>
<td></td>
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</table>

*One patient did not have any viable oocyte at the time of retrieval*
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<td>0.002</td>
</tr>
</tbody>
</table>

|                                |                          |                     |                                                     |         |
| Perenatality rate and T/E2 (IU/mL) | 6.9 ± 0.27              | 6.8 ± 0.17          | 0.14 (-0.06, 0.34)                                 |         |
| Day of transfer                |                          |                     |                                                     |         |
| Day 2                          | 8 (100%)\(^a\)           | 6 (67%)             |                                                     |         |
| Day 3                          | 0                        | 3 (33%)             |                                                     |         |
| Embryos Transferred            | 1.6 ± 1.2                | 3.4 ± 1.6           | 1.8 (0.5, 3.0)                                     | 0.013   |
| Implantation Rate              | 0                        | 6.5 %               |                                                     |         |
| Clinical Pregnancy Rate        | 0                        | 2 (22.2%)           |                                                     |         |

\(^a\) One patient did not have any viable oocyte at the time of retrieval

- Unpowered small samples size
- Retrospective nature
- Lack of demonstration of better ovarian suppression with this protocol
  - No data on endogenous FSH, LH and E2 levels prior to stimulation
Delayed Start Versus Conventional GnRH Antagonist Protocol in Poor Responders Pretreated With Estradiol in Luteal Phase: A Randomized Controlled Trial

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Abstract

Objective: To compare the new delayed start protocol against the conventional gonadotropin (Gn)-releasing hormone antagonist protocol in poor responders (PORs). Study Design: A total of 160 women with poor response to previous in vitro fertilization (IVF) cycle were randomized either to start Gn then Cetrotide 0.25 subcutaneously (sc) added when leading follicle (DF) reach >12 mm or Cetrotide 0.25 mg sc started first from day 2 to day 8 then Gn therapy was added and Cetrotide restarted when DF reach >12 mm. Results: There was a statistically significant difference between conventional and delayed start protocols regarding the needed dose of Gn for stimulation (4368 ± 643 and 3798 ± 515), level of estradiol (E2; 778 ± 371 and 1076 ± 453), and endometrial thickness at human chorionic gonadotropin triggering (8.6 ± 1.8 and 9.8 ± 1.9), the number of DF (3.4 ± 1.5 and 4.9 ± 2.1), the number of retrieved follicles (2.4 ± 2.1 and 4.3 ± 2.5), and successful embryo transfer (13 vs 16), respectively (P < .05). There was a highly statistically significant difference between the 2 study groups regarding the number of oocytes fertilized (1.2 ± 2.0 vs 3.3 ± 1.4), metaphase II oocytes (0.9 ± 1.0 vs 2.7 ± 1.6), and grade I embryos (0.7 ± 0.9 vs 2.1 ± 1.1; P < .001). The chemical pregnancy, clinical pregnancy, and abortion rate showed a statistically significant difference between the 2 study groups (P value .003 and .006, respectively). Conclusion: Delayed start protocol significantly improved clinical pregnancy rate and IVF cycle parameters in PORs.
AROMATASE INHIBITORS

• Aromatase inhibitors, such as letrozole, significantly suppress plasma estrogen levels by competitively inhibiting the activity of the aromatase enzyme.

• Centrally, aromatase inhibitors release the hypothalamic/pituitary axis from estrogenic negative feedback, increase the secretion of FSH by the pituitary gland, stimulate follicle growth, and, thereby, can be used for ovulation induction.

• Aims to increase ovarian response to stimulation by recruiting more antral follicles by its flare effect.
In patients with estrogen-sensitive cancers, the main advantage of adding daily letrozole to gonadotropins in ovarian stimulation protocols is to decrease serum estradiol levels closer to that observed in natural cycles (i.e., estradiol < 500 pg/ml) without affecting oocyte or embryo yield.
AROMATASE INHIBITORS

• BREAST CANCER
• ENDOMETRIAL ADENOCARCINOMA
• ENDOMETRIAL STROMAL CANCER
• SLE
• POOR RESPONDERS
AROMATASE INHIBITORS

Diagram:
- GnRH agonist
- GnRH antagonist
- r-FSH
- Letrozole

Timeline:
- Day 2
- Day 4
- Retrieval

Time of menstrual cycles (days)
• The short-term follow-up of patients with breast cancer, who have undergone ovarian stimulation with letrozole along with gonadotropins for fertility preservation, has not shown to raise the risk of breast cancer recurrence.

• In addition, COS with aromatase inhibitors in combination with gonadotropins was also safely used for embryo cryopreservation in patients with endometrial cancer.

AROMATASE INHIBITORS

• There was no evidence of a decline in relapse-free survival rates in the two studies of women with breast cancer who received COH with letrozole co-administration compared with women who did not undergo fertility preservation procedures.

• The largest of these studies reported recurrences in 6/120 (5.0%) women who received COH plus letrozole compared with 12/217 (5.5%) women who did not undergo COH (mean follow-up 5.0 versus 6.9 years; hazard ratio for recurrence 0.77, 95%CI 0.28-2.13).

RODGERS RJ ET AL. Hum Reprod. 2017
Oktay et al JCEM 2016
Conclusions regarding women with breast cancer who received tamoxifen during COH could not be made due to insufficient data. Peak oestradiol concentrations (338-829 pg/ml) were suppressed by letrozole when commenced on Days 2-3, with no decrease in oocyte yield.

Tamoxifen does not suppress oestradiol concentrations, but may convey protection via its inhibitory action on the oestrogen receptor.
AROMATASE INHIBITORS

• The co-administration of 5 mg of letrozole daily commencing on Day 2 and continuing throughout COH is recommended as it reduces peak oestradiol concentrations without significantly decreasing oocyte yield.

• The use of a GnRH agonist trigger is beneficial as oestradiol concentrations rapidly decrease post-administration and rates of ovarian hyperstimulation are lower than with an hCG trigger, without a corresponding reduction in clinical pregnancy or live birth rates in cryopreservation cycles.

• The protective effect of tamoxifen has not been evaluated although theoretically may be of benefit due to its action on the oestrogen receptor.

RODGERS RJ ET AL. Hum Reprod. 2017 May 1;32(5):1033-1045
In the poor-responder population, it is unclear whether there was any difference in rates of live birth (RR 1.16, 95% CI 0.49 to 2.79, 2 RCTs, n = 357, $I^2 = 38\%$, low-quality evidence) or clinical pregnancy (RR 0.85, 95% CI 0.64 to 1.12, 8 RCTs, n = 1462, $I^2 = 0\%$, low-quality evidence) following CC or Ltz with or without gonadotropin versus gonadotropin and GnRH protocol.

This means that for a typical clinic with a 5% LBR in the poor responders using a GnRH protocol, switching to CC or Ltz protocols would be expected to yield LBRs between 2% to 14%.

To date, the data do not indicate an elevated rate of abnormality at birth after luteal phase stimulation.
Ovarian Feedback on the Hypothalamus and Pituitary

- **Negative Feedback**
- **Progesterone**

  Progesterone has a profound effect on gonadotropin secretion that manifests at the hypothalamic level through slowing of pulsatile GnRH secretion.

  This effect requires estrogen priming, likely through upregulation of progesterone receptors in the hypothalamus.
• PPOS is a new ovarian stimulation regimen based on a freeze-all strategy that uses progestin as an alternative to a GnRH analog for suppressing a premature LH surge during the follicular phase.

• General IVF targets
  • NO differences between CPR, LBR
  • No premature LH surge
• Human menopausal gonadotropin (hMG; 225 iu per day) and MPA (group A, 10 mg per day; group B, 4 mg per day) were started simultaneously from cycle day 3 onwards.

• Ovulation was co-triggered by human chorionic gonadotropin (hCG; 1000 iu) and gonadotropin-releasing hormone agonist (GnRH agonist; 0.1 mg) when dominant follicles matured.

• Viable embryos were cryopreserved for later frozen embryo transfer (FET) in both groups.
Fertility and Assisted Reproduction

The pregnancy outcome of progestin-primed ovarian stimulation using 4 versus 10 mg of medroxyprogesterone acetate per day in infertile women undergoing *in vitro* fertilisation: a randomised controlled trial

J Dong, Y Wang, WR Chai, QQ Hong, NL Wang, LH Sun, H Long, L Wang, H Tian, QF Lyu, XF Lu, QJ Chen, YP Kuang

New application of dydrogesterone as a part of a progestin-primed ovarian stimulation protocol for IVF: a randomized controlled trial including 516 first IVF/ICSI cycles

Sha Yu, Hui Long, Hannah Ya-ning Chang, Yali Liu, Hongyuan Gao, Jing Zhu, Xinxin Quan, Qifeng Lyu, Yanping Kuang, Ai Ai


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CONCLUSION

• Indications for unconventional stimulation protocols extend beyond cancer.
  – Random-start ovarian stimulation
  – Letrozole IVF
  – PPOS

  – Insufficient data to draw a conclusion on CPR or LBR.
THANK YOU