Secondary fertility preservation after cancer therapy – which stimulation protocols are most effective and least expensive in women with reduced ovarian reserve?

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Background: Although primary fertility preservation before cancer treatment remains the most common option, secondary fertility preservation — the cryopreservation of gametes following cancer therapy — is gaining relevance. This approach is particularly important for patients who were unable to undergo fertility preservation prior to cancer treatment, or for whom the need for fertility preservation is controversial, such as adolescents. However, a major challenge in secondary fertility preservation is the reduction in anti-Mullerian hormone (AMH) levels following gonadotoxic cancer therapies. This complicates ovarian stimulation and increases costs. Therefore, it is essential to select the most time- and cost-effective stimulation protocol.

Aims: A post hoc analysis was conducted on an international multicentre study that included 3 Swiss and 5 German infertility centres. The study covered various IVF treatment protocols, including natural cycles (NC), minimal stimulation using oral agents such as clomiphene citrate or aromatase inhibitors alone (Min Stim), minimal stimulation combined with oral agents plus 75–100 IU of gonadotropins (Min Stim+), and full stimulation protocols (Full Stim). Only patients with an AMH concentration of ≤2 ng/mL were included and were categorised according to their AMH concentration: <0.5 ng/mL, 0.5-≤1.0 ng/mL and 1.0-≤2.0 ng/mL. The analysis comprised two hypothetical treatment scenarios: (1) performing up to 10 stimulation cycles, and (2) collecting a total of at least 10 metaphase II (MII) oocytes. The expected cumulative costs (in euros) per scenario were calculated for each protocol and AMH category. The total number of oocytes collected was estimated using a generalised linear model with a negative binomial distribution. This model predicted the number of oocytes for each treatment protocol and AMH group over 1 to 10 cycles (scenario 1). Based on these results, the number of cycles required to collect a minimum of 10 MII oocytes was calculated (scenario 2).

Ethical approval was obtained from the leading ethics committees in Switzerland (Bern, KEK ID 2021-01689) and Germany (Baden-Württemberg (ID F-2024-068), Niedersachsen (ID Grae/080/2024), Bavaria (ID mb24043), Nordrhein-Westfalen (ID 2024 194)) for all participating centres.

Results: A total of 2,407 ICSI cycles from 1,194 patients were included in the study. These treatments were performed between 01/01/2022 and 31/03/2023. Although the statistical analysis is ongoing, preliminary results from scenario 2 suggest the following outcomes: to collect 10 oocytes, in women with AMH <0.5 ng/ml, the protocols requiring the fewest cycles are Full Stim (n=3) and Min Stim+ (n=5) and the least expensive strategies are Min Stim (Euro 4.240,-) and Min Stim+ (4925,-). For women with AMH levels between AMH 0.5 and ≤1 ng/ml the respective protocols are Full Stim (n=2) and Min Stim+ (n=4), as well as Min Stim (3.276,-) and Min Stim+ (3.980,-). In women with AMH 1 - ≤2 ng/ml the respective protocols are Full Stim (n=1.5) and Min Stim+ (n=3) as well as Min Stim+ (3.036,-) and Min Stim (3.759,-).

Conclusion: Secondary fertility preservation requires treatment regimens tailored to the individual, taking into account both AMH concentrations and financial implications. This is because secondary fertility preservation is not reimbursed in most countries. Furthermore, given the necessity for multiple stimulation cycles, it is essential to minimise the patient's treatment burden.

In this context, for women with reduced ovarian reserve, minimally stimulated (Min Stim/Min Stim+) protocols may offer the most advantageous balance between reducing stimulation cycles and controlling costs.