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Gonadotropin-Releasing Hormone Agonist Debate

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The recent publications by Demeestereet a land the accompanying editorial in the journal of clinical oncology are intriguing [1,2]. We agree with the authors' statement: "… pregnancy is the most accurate …for evaluating the efficiency of fertility preservation." We have shown that GnRH a increased spontaneous conceptions (P <0.006), in addition to preserving Cyclic Ovarian Function (COF) (OR = 6.87) [3], in a large group of young women followed up for up to two decades. Ninety patients (62%) conceived 178 times in the GnRHa group *vs.* 31 patients experiencing 55 pregnancies (42%) in the controls (P <0.0003), generating 131 and 41 newborns (P <0.01), respectively [3]. Spontaneous pregnancies occurred in 58% of the survivors in the GnRHa group, vs 34.9% of the controls (P = 0.009). Similarly, two recent RCT's publications, in the NEJM and JAMA [cited in 1] assessed the efficacy of GnRHa reporting promising data on fertility outcomes [1]. Both studies found significant reduction in premature ovarian failure (POF) in the GnRHa arms (OR: 0.28-0.3; P <0.001-0.04) [3].

The authors [1] mention their study limitations: dropout rate of 50%, and 25% loss of follow-up or data unavailability. Although the original study "mandated the accrual of 157 patients to ensure a power of 80% and a type error I probability of 5%, enrolment was discontinued after the assignment of129 patients," but only 63 patients were evaluated for POF, 31-32 in each arm, in 15 centers (1-3 patients/arm/center). Furthermore, five pregnancies occurred in patients with protocol-defined POF of "one FSH >40U/L measurement" challenging the accuracy of POF definition, and the resulting conclusions.

Indeed, the study initially did not find a difference in POF rate after one year [4], but two years follow-up [5] claimed: "… the number of patients who totally restored their ovarian function was significantly higher in the GnRHa group (P = 0.049) confirming results of AMH", (mean AMH was 1.4±0.35 ng/ml in the GnRHa arm *vs.* 0.5 ± 0.15ng/ml in the controls (P <0.04)) [4]. The small number of the evaluated patients (type-I error) may explain the "negative" results after one year [4], the pendulum swinging to "positive" result at 2 years [5], and again switching back to negative conclusion at 5 years[1].

Relevant to this equivocal issue, a publication [6] from one of the previous opponents to GnRH-a, has found that the use of GnRHa during chemotherapy has significantly increased the probability to become pregnant (OR = 12.87 P = 0.001); They [6], "…found strong (OR (12<indirect evidence supporting the prophylactic use of GnRH-a in early unfavorable HL, concluding: "… the use of GnRH analogues during therapy is a strong, independent, and a highly significant predictor of pregnancies."

In contradiction to the unbalanced editorial [2] the two recently published experts' opinion, 14th St Gallen international conference and expert consensus [7,8], support the use of GnRHa, stating that GnRHa therapy during chemotherapy proved effective to protect against POF and preserve fertility[7,8], with the highest level of evidence, IA [7]. They state that the GnRHa co treatment increased the rate of subsequent successful pregnancies and did not compromise disease outcomes [7,8].

Oktay and Bedoschi [2] claim that none of the studies favoring GnRHa effect for fertility preservation was blinded or placebo controlled, therefore unacceptable. On the other hand, they [2] claim that the successful reports on ovarian cryopreservation should lead to accepting this method as an unequivocally established method for fertility preservation. How many of these reports were

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"blinded or placebo controlled" or even RCT's? None. What is the justification of their double standard?

Furthermore, Oktay and Bedoschi [2] claim that primordial follicles do not have FSH receptors and their growth is unaffected by GnRHa. In contradiction, Zheng et al. [9] demonstrated FSH receptorm RNA expression, by RT-PCR, in primordial follicles. More recently, Bhartiya and Singh [10], have identified two distinct populations of stem cells including very small embryonic-like stem cells (VSELs) and ovarian stem cells in OSE, responsible for neo-oogenesis and Primordial Follicle (PF) assembly in adult life, being modulated by FSH via its alternatively spliced receptor variant FSH-R_3. If indeed FSH-R_3 (lacking exon 10) is the key player to mediate FSH action on stem cells, one could easily explain why the extensive studies undertaken to search for mutations in exon 10 of FSH receptor have failed. Failure to detect FSH receptors on PF's incorrectly suggested that initial PF growth is GN independent. However, the primers used for rt-PCR were selected from exon 10 whereas PF's express FSH-R_3 that lacks exon 10.

Due to these and several other inaccurate points, these publications [1,2], are unconvincing and intriguing. The recent publication [11], by several leaders in fertility preservation seems to be in keeping with our opinion.

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