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Critical Care for Young Women before Chemotherapy: Preserving Fertility Using *GnRH* Agonists

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Capsule

The pro and con using *GnRH*-agonist for endocrine suppression before critical care gonadotoxic chemotherapy in young female patients is summarized.

Introduction

The increase in young age malignancy, along with improvement in remote survival has generated a global interest in the endeavors for fertility preservation in young female patients treated by gonadotoxic chemotherapy.

The remote effects of malignancy treatment have gained a global ubiquitous interest among fertility specialists, gynecologists, oncologists, hematologists, rheumatologists, pediatricians, family physicians and actually all health care providers, and the endeavor for fertility preservation and minimizing iatrogenic ovarian failure and subsequent infertility, caused by gonadotoxic chemotherapy, assumes utmost priority.

Although numerous papers on this issue have been published, numerous equivocal points still require elaboration [1-17].

Up to date 21 studies [15 retrospective and 6 RCT] have reported on 2328 patients receiving *GnRHa* treatment before and along chemotherapy, demonstrating a significant diminution in premature menopause rate in survivor's vs. 8 publications reporting on 509 patients, where this treatment did not bring about a significant decrease in POF rate.

The patients who received *GnRHa* adjuvant treatment along gonadotoxic chemotherapy resumed regular menses and normal ovarian function in about 90% of cases as compared to 40% of those who received only chemotherapy, with a pregnancy rate ranging 20-70% in the *GnRHa* co-treated patients.

Furthermore, thirteen recent metaanalyses of RCT's, and two recent international expert consensus meetings [1-3,13,14] have critically summarized the issue, concluding that *GnRHa* adjuvant cotreatment along chemotherapy significantly minimizes the risk of POF and increases pregnancy rate in survivors [1-17].

Several methods are currently experienced for fertility preservation in young female patients despite gonadotoxic chemotherapy: ovariopexy, cryopreservation of embryos, unfertilized oocytes, and ovarian fragments, and endocrine ovarian suppression using *GnRHa* cotreatment [1-8]. However, none of the experienced modalities is perfect and none promises future fertility. IVF and cryopreservation of embrya, the only non-investigational, clinically unequivocal method, requires postponing chemotherapy for about two weeks, despite using the recently proven random start efficiency.

More intriguingly, although cryopreservation of ovarian tissue and later auto-transplantation has successfully brought about over 50 deliveries, it is not completely safe and successful; the danger that the cryopreserved-thawed ovarian pieces might harbor neoplastic cells or stem cells, that could reintroduce malignancy in a cured patient has been suggested [1,18-21]. Indeed, auto-transplantation of cryopreserved-thawed ovarian fragments taken from leukemia patients may cause disease recurrence, due to possible ovarian contamination with malignant cells [18,19].

Similarly, gonadal involvement with malignant cells in Ewing sarcoma or Hodgkin disease has been also published, despite appreciation that these disease do not metastasize to the ovaries [20,21]. Even more alarming, Kyono et al. [22] have discussed the potential indications for ovarian auto-transplantation based on 5,571 post-mortem findings of young female patients, younger than 40. Intriguingly these investigators detected ovarian involvement with malignancy in 8-55% of overall autopsies and 4-13% gonadal involvement in lymphoma, reaching the conclusion that no reliable method exists to completely rule out possible residual malignancy in the cryopreserved ovarian fragments, and therefore reimplantation is not completely safe [22].

An “artificial ovary” whereby primordial follicles might be in-vitro matured [IVM] to fertilizable M-II ova is a future endeavor of utmost clinical potential, however several obstacles have to be overcome, and thus this promising technology is not clinically available yet [1,6].

Consequently, *GnRHa* adjuvant co-treatment has been practiced in many centers for diminution the gonadotoxic effects of chemotherapy [1-17] by mimicking a prepubertal hormonal milieu, with the logic and philosophy that preventing premature ovarian failure [POF] in survivors is preferable to treating it, following the dictum: "an ounce of prevention is worth a pound of cure" [1,5]. Furthermore, 13 recent metaanalyses have concluded that GnRHa use is beneficial and can decrease POF occurrence in survivors [1-17].

The only prospective randomized study where histological count of the follicles has been done, which obviously cannot be performed in women, has been conducted in Rhesus monkeys, evaluating the follicular loss after exposure to an alkylating agent alone or in parallel to *GnRHa* cotreatment [23]. During the cyclophosphamide alone exposure, 64.6 ± 2.8% of the overall primordial follicles were destroyed compared to only 28.9 ± 9.1% in the *GnRHa*+ cyclophosphamide group (P=0.05). The daily decline in follicular number was 0.12 ± 0.012% in the cyclophosphamide group compared to 0.057 ± 0.019% (P=0.05) in the *GnRHa +* cyclophosphamide group [23]. These investigators reached the conclusion that *GnRHa* co-treatment could protect the ovary against cyclophosphamide-induced gonadotoxicity.

Two recent, large, and convincing prospective RCT's were published in the last year [2,16,24]. The POEMS-SWOG S0230 study enrolled only HR-negative breast cancer patients [24]; whereas most patients in the PROMISE-GIM6 [16] study were HR positive. Both RCT's demonstrated a statistically significant, 70-72% reduction in ovarian failure rate in the *GnRHa* arms, (OR: 0.28-0.30; P=0.001-0.04) [4,8,9,15] (OR: 0.30; P=0.04). Moreover, the pregnancy rate was significantly increased by GnRHa (OR: 2.45; P= 0.03) [2,16].

Long-term evaluation of the PROMISE-GIM6 study, after a median follow-up of 7.3 years (range, 6.3-8.2 years) [16] has shown a 5-year cumulative menstrual resumption of 72.6% (95% CI, 65.7%-80.3%) among the GnRHa group and 64% (95% CI, 56.2%-72.8%) among the controls (age-adjusted HR, 1.48 [95% CI, 1.12-1.95]; P=0.006) [9] with no difference in the 5 year disease free survival [DFS] [2,16]. In the POEMS-SWOG S0230 study, a NIH-sponsored, prospective RCT trial, in which 257 premenopausal breast cancer patients received chemotherapy with or without GnRHa [24], the GnRHa-treated patients had better-preserved ovarian function across multiple endpoints and improved fertility (more pregnancies) than the controls [24]. Unexpectedly, the GnRHa cotreatment led to more favorable disease free survival (DFS) and overall survival (OS) rates vs. the chemotherapy alone controls [24]. Two years after chemotherapy, the POF rate was 22% for the standard chemotherapy arm compared with only 8% for the *GnRHa* arm (OR=0.30, 95% CI [0.09, 0.97]; P=0.04) [24]. Successful pregnancy was achieved by 12/18 women who attempted pregnancy in the chemotherapy alone group compared to 22/25 successful pregnancies in the *GnRHa* treated patients (adjusted OR 2.45; P=0.03). In addition, women in the *GnRHa* group gave birth to 18 babies versus 12 in the standard chemotherapy group. In an unexpected and surprising finding, the 4-year mortality rate in the *GnRHa* group was significantly lower than in the control group (P=0.05) [24].

Pertinent to this equivocal issue, a publication [25] from a former opponent to *GnRH-a* treatment for fertility preservation, has concluded that the use of *GnRHa* during gonadotoxic chemotherapy has also significantly increased the probability to conceive [OR= 12.87; P=0.001].

Furthermore, these investigators [25], *"…found surprisingly strong (OR (12 indirect evidence supporting the prophylactic use of GnRHa in women receiving therapy for early unfavorable HL"*. They have, therefore, concluded, *"…the multivariate analysis in the present study reveals that the use of GnRH analogues during therapy is a strong, independent, and a highly significant predictor of pregnancies."* This publication also supports the conclusion that *GnRHa* treatment can preserve ovarian function and fertility.

Another, apparently not supporting study, by Demeestere et al. [26], who initially did not find a difference in POF rate after 1 year, have presented an abstract [at the IIIrd meeting of the International Society for Fertility Preservation in Spain in November 2013], whereby at 2 years follow-up of the same patients, [26]: *“…the number of patients who totally restored their ovarian function was significantly higher in the GnRHa group (P= 0.049)…”* confirming their previously published results of higher AMH in the *GnRHa* arm vs controls [1.5 ng/mL vs 0.5 ng/mL, respectively]. This supports our and others' published explanation that short follow-up may be responsible for the discrepancy between studies and lead to incorrect conclusions [1-10].

GnRHa Controversy - Pros and Cons

Both societies, the American Society of Clinical Oncology [ASCO] and the American Society for Reproductive Medicine [ASRM] concluded that there are not unequivocal data proving that *GnRHa* preserves fertility [27,28]; therefore, *GnRHa* is not considered a proven effective method of fertility preservation [27,28]. However, these conclusions are not up-to-date since they did not evaluate the recent RCT's, metaanalyses, and international expert opinion committees, recently published [1-17,24].

Many investigators consider cryopreservation of ovarian tissue as an established method of fertility preservation, despite the fact that no randomized trials assessed its role in preserving fertility, the evidence based results for such a consideration is considered low, according to Fleisher et al. [29], being supported by nonrandomized, case-control or observational studies. On the contrary, GnRHa adjuvant co-treatment efficiency has been documented in both randomized trials and many case-control studies [1-17,24].

A raised argument against *GnRHa* cotreatment [30] claimed that: "A clinical example for why gonadal suppression may not protect ovaries is the fact that prepubertal children receiving high-dose chemotherapy given before hematopoietic stem cell transplantation still suffer from ovarian failure".

However, Remerand et al. [31] reported 4 spontaneous gestations and normal deliveries in a patient after high dose Busulphan and Cyclophosphamide [Bu-Cy] conditioning [the most gonadotoxic combination] and BMT, at 4 years of age, suggesting that normal spontaneous conceptions can occur in women who had stem cell transplantation [SCT] and aggressive conditioning prepubertally. Similarly, we have described the only published case report of several spontaneous pregnancies and repeated spontaneous gestations and deliveries of normal neonates after two autologous BMT's [ten year apart] and *GnRHa* co-treatment, in a post-pubertal lymphoma patient, demonstrating that the induction of the prepubertal milieu using GnRHa adjuvant could have contributed to the preserved fertility despite repeated stem cell transplantations [11]. Only 0.6% of women undergoing SCT may experience pregnancy after one SCT, as reported by a European survey, involving 37,362 women [32]. Thus, the estimated chance of conception after two SCT's are very low (0.006 x 0.006=0.000036) [10]. Similarly, another publication [33] on 619 patients, found that only 3% experienced pregnancy after one SCT. Thus, based on these published results, the calculated odds for conception after two SCTs are 0.03×0.03=0.0009, less than 1:10,000 [32,33]. The *GnRHa* co-treatment along the aggressive chemotherapy induced a prepubertal hormonal milieu, decreasing the gonadotoxic effect and augmenting the chance of ovulation, spontaneous pregnancies, and successful deliveries [10].

Another argument, raised by the opponents to *GnRHa* co-treatment, is that 8% of the women exposed to prepubertal chemotherapy may suffer POF, contradicting the rationale for simulating the prepubertal milieu. Indeed, several publications, [34-36] have shown that survivors of prepubertal malignancy may experience premature menopause before 40 years in 8% of cases, vs. 1% in the general population. The 8% risk of POF in such patients is in similar to the 7%–13% POF rate in female patients in their reproductive age treated with *GnRHa* along the gonadotoxic chemotherapy compared to a 30-60% risk of POF in patients exposed to chemotherapy without the agonist [1-17]. Not only that this argument does not contradict the rationale for *GnRHa* use; it can strengthen the pathophysiological logic of endocrine ovarian suppression for inducing a temporary pre-pubertal milieu.

Another claimed concern whereby the *GnRHa* is that it may reduce the efficiency of chemotherapy. A contradiction to this theoretical and unsubstantiated argument was shown in the Lancet meta-analysis [37], based on almost 12 thousand women with breast cancer. This study has found that adding *GnRHa* to tamoxifen, chemotherapy, or both decreased cancer recurrence by 12.7% (P=0.02) and patients' death by 15% (P=0.03). Most recently, the ASCO convened an update panel conducting a systematic review of RCT's investigating ovarian suppression, in order to update the ASCO adjuvant endocrine therapy guideline based on emerging data concerning the benefits and risks of ovarian suppression in addition to standard adjuvant therapy in premenopausal women with estrogen receptor–positive breast cancer [38]. "The panel recommends that higher-risk patients should receive ovarian suppression in addition to adjuvant endocrine therapy. Women with stage II or III breast cancers who would ordinarily be advised to receive adjuvant chemotherapy should receive ovarian suppression with endocrine therapy. The panel recommends that some women with stage I or II breast cancers at higher risk of recurrence who might consider chemotherapy may also be offered ovarian suppression with endocrine therapy. Ovarian suppression may be administered with either tamoxifen or aromatase inhibitor" [38]. These, along many other publications, contradict the unsubstantiated hypothetical speculation whereby *GnRHa* might decrease chemotherapy efficiency. Furthermore, the publications by our and other groups of Del-Mastro and Recchia, as well as the recent POEMS]-SWOG S0230 RCT, and expert opinion committees demonstrate either similar, or improved survival rates with *GnRHa* compared to the controls, without the agonist [1-5,12-17,24,39]. We have treated by now over 300 young female patients with *GnRHa* along the gonadotoxic chemotherapy for different indications and the survival rate was similar to the patients undergoing comparable treatment without *GnRHa* [1,3-10].

Whereas none of the experienced methods for fertility preservation is perfect and promises subsequent fertility preservation, several modalities can be combined. Maximizing patients' odds for future fertility may necessitate the combination of ovarian cryopreservation, *GnRHa* adjuvant, and IVF-follicular aspiration. All these methods need to be offered to all young women before gonadotoxic chemotherapy, including BMT [1-10,40], since it has been demonstrated that *GnRHa* cotreatment is effective not only against usual chemotherapy but also for lymphoma patients undergoing BMT [1,10,40]. Furthermore, *GnRHa* can prevent the thrombocytopenia-associated menorrhagia, which is a frequent complication of chemotherapy [1-10]. Increasing pregnancy rate in survivors has been significantly demonstrated in three continents, by three different groups: in the US, America [24], in the UK, Europe [41], and in Israel, Asia [1].

Conclusion

In conclusion, we suggest offering all the patients, the three avenues for fertility preservation: cryopreservation of embryo, ova, ovarian tissue and *GnRHa* [1], even in high-risk patients as leukaemia [1,10]. The rationale leading to this policy is in the hope that in a few years, the "artificial ovary"– IVM technology of primordial follicles to mature Graaffian follicles containing M-II fertilizable oocyte may become possible [1], bypassing the ovarian auto-transplantation need, in those patients who turn prematurely menopausal. Although this technology is not available yet in human, the previous success in rodents, and the three-dimensional follicle culture in alginate gel, may

hopefully become real in several years [1-6]. Therefore, all the possibilities should be offered to these young patients.

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