女性 IVF/ICSI 个体化 FSH 给药方案，以卵巢储备测试为基础的：多中心试验和成本-效果分析

Individualized FSH dosing based on ovarian reserve testing in women starting IVF/ICSI: a multicentre trial and cost-effectiveness analysis.

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研究问题：女性 IVF 或者 ICSI 周期中，基于窦性卵泡计数（AFC）的个体 FSH 剂量与标准 FSH 卵泡注射剂量的活产率和或成本-效果分析有差异吗？

总结：女性开始 IVF/ICSI 周期时，基于 AFC 的 FSH 剂量不能显著提高活产率或者降低成本（对比标准 FSH 计量使用）。

目前已知：在 IVF 或 ICSI 周期中，卵巢储备测试经常被用来指导 FSH 用量，其目的是促使卵巢功能正常并最大化提高活产率。但是对于成本分析，目前没有强有力证据。

实验设计，范围，持续时间：在 2011 年 3 月至 2014 年 3 月，我们对 IVF/ICSI 进行多中心前瞻性队列研究，里面含有 2 个随机对照实验研究。基于 AFC，女性患者进入 RCTs 一组(RCT1: AFC < 11; RCT2: AFC > 15)，或者对照组(AFC 11-15).。首要考虑结果是随机实验后，在 18 个月内持续妊娠，活产（24 周后至少有一例活胎）。对照组中将体重 0.5 与随机对照实验组合并，进行数据分析。分析这两组治疗方式的效果和成本。

参与者，材料，方法：在 2 组 RCTs 中，女性患者进行随机分配(RCT1:450/225 IU, RCT2:100 IU)或者根据 FSH 剂量(150 IU)。在对照组中的女性患者接受的是标准剂量(150 IU)。对于 RCT1 组，激素剂量是按照预先指定的标准进行。对于 RCT2 组激素剂量 2 组均可。2 组的成本-效果进行评估。

主要结果：我们评估了 1515 位女性患者，其中 483（31.9%）在对照组，511（33.7%）在 RCT1，521（34.4%）在 RCT2。活产率为 420/747 (56.3%)女性在个体化策略中，447/769 (58.2%)女性在标准策略中。个体化策略会更贵(delta costs/woman = € 275 (95% CI, 40 to 499))。个体化策略会减少 OHSS 的发生率，并降低治疗 OHSS 的费用(costs saved/woman were €35)。

实验限制：尽管本实验有严格限制，但是 AFC 可能会有不同观察者之间差异。此外，虽然有严格取消标准要求，但是对于个体剂量组（特别是不良反应）不能被直接排出，在接下来的周期中，允许剂量有小范围调整。但是，开放式实验设计并未掩盖个体化差异的优势；在不同策略中，第一个周期的活产率和累积活产率并未显示有明显差异。越来越多的人同意使用 GnRH 拮抗剂联合治疗，特别是有高反应的患者，在这项研究中几乎有 80%的妇女使用促性腺激素释放激素激动剂。因此，在这些女性中，在 AFC 和 AMH 的分析研究对垂体的抑制。由于促性腺激素释放激素激动剂使用过程中，AFC 和卵巢反应之间的相关性不会受到影响，这可能不会影响分析。

本实验的应用：不应该过度追求在 IVF/ICSI 周期中进行个体化 FSH 剂量调控，因为它不能提高活产率并且它会增加花费。女性患者有正常的月经周期，在进行 IVF/ICSI 周期中，应推荐进行标准 FSH 剂量，150IU/天。但是在高反应患者中个体化给药安全管理有待进一步研究。

关键词：FSH；ICSI;IVF；anti-Müllerian hormone；窦卵泡计数；成本-效果分析；个体化；活产率；卵巢反应；卵巢激素测试；

Abstract

STUDY QUESTION:

Is there a difference in live birth rate and/or cost-effectiveness between antral follicle count (AFC)-based individualized FSH dosing or standard FSH dosing in women starting IVF or ICSI treatment?

SUMMARY ANSWER:

In women initiating IVF/ICSI, AFC-based individualized FSH dosing does not improve live birth rates or reduce costs as compared to a standard FSH dose.

WHAT IS KNOWN ALREADY:

In IVF or ICSI, ovarian reserve testing is often used to adjust the FSH dose in order to normalize ovarian response and optimize live birth rates. However, no robust evidence for the (cost-)effectiveness of this practice exists.

STUDY DESIGN, SIZE, DURATION:

Between May 2011 and May 2014 we performed a multicentre prospective cohort study with two embedded RCTs in women scheduled for IVF/ICSI. Based on the AFC, women entered into one of the two RCTs (RCT1: AFC < 11; RCT2: AFC > 15) or the cohort (AFC 11-15). The primary outcome was ongoing pregnancy achieved within 18 months after randomization resulting in a live birth (delivery of at least one live foetus after 24 weeks of gestation). Data from the cohort with weight 0.5 were combined with both RCTs in order to conduct a strategy analysis. Potential half-integer numbers were rounded up. Differences in costs and effects between the two treatment strategies were compared by bootstrapping.

PARTICIPANTS/MATERIALS, SETTING, METHODS:

In both RCTs women were randomized to an individualized (RCT1:450/225 IU, RCT2:100 IU) or standard FSH dose (150 IU). Women in the cohort all received the standard dose (150 IU). Anti-Müllerian hormone (AMH) was measured to assess AMH post-hoc as a biomarker to individualize treatment. For RCT1 dose adjustment was allowed in subsequent cycles based on pre-specified criteria in the standard group only. For RCT2 dose adjustment was allowed in subsequent cycles in both groups. Both effectiveness and cost-effectiveness of the strategies were evaluated from an intention-to-treat perspective.

MAIN RESULTS AND THE ROLE OF CHANCE:

We included 1515 women, of whom 483 (31.9%) entered the cohort, 511 (33.7%) RCT1 and 521 (34.4%) RCT2. Live births occurred in 420/747 (56.3%) women in the individualized strategy and 447/769 (58.2%) women in the standard strategy (risk difference -0.019 (95% CI, -0.06 to 0.02), P = 0.39; a total of 1516 women due to rounding up the half integer numbers). The individualized strategy was more expensive (delta costs/woman = € 275 (95% CI, 40 to 499)). Individualized dosing reduced the occurrence of mild and moderate ovarian hyperstimulation syndrome (OHSS) and subsequently the costs for management of these OHSS categories (costs saved/woman were € 35). The analysis based on AMH as a tool for dose individualization suggested comparable results.

LIMITATIONS, REASONS FOR CAUTION:

Despite a training programme, the AFC might have suffered from inter-observer variation. In addition, although strict cancel criteria were provided, selective cancelling in the individualized dose group (for poor response in particular) cannot be excluded as observers were not blinded for the FSH dose and small dose adjustments were allowed in subsequent cycles. However, as both first cycle live birth rates and cumulative live birth rates show no difference between strategies, the open design probably did not mask a potential benefit for the individualized group. Despite increasing consensus on using GnRH antagonist co-treatment in women predicted for a hyper response in particular, GnRH agonists were used in almost 80% of the women in this study. Hence, in those women, the AFC and bloodsampling for the post-hoc AMH analysis were performed during pituitary suppression. As the correlation between AFC and ovarian response is not compromised during GnRH agonist use, this will probably not have influenced classification of response.

WIDER IMPLICATIONS OF THE FINDINGS:

Individualized FSH dosing for the IVF/ICSI population as a whole should not be pursued as it does not improve live birth rates and it increases

costs. Women scheduled for IVF/ICSI with a regular menstrual cycle are therefore recommended a standard FSH starting dose of 150 IU per day. Still, safety management by individualized dosing in predicted hyper responders is open for further research.

KEYWORDS:

FSH; ICSI; IVF; anti-Müllerian hormone; antral follicle count; cost-effectiveness; individualized; live birth; ovarian reserve; ovarian reserve test.