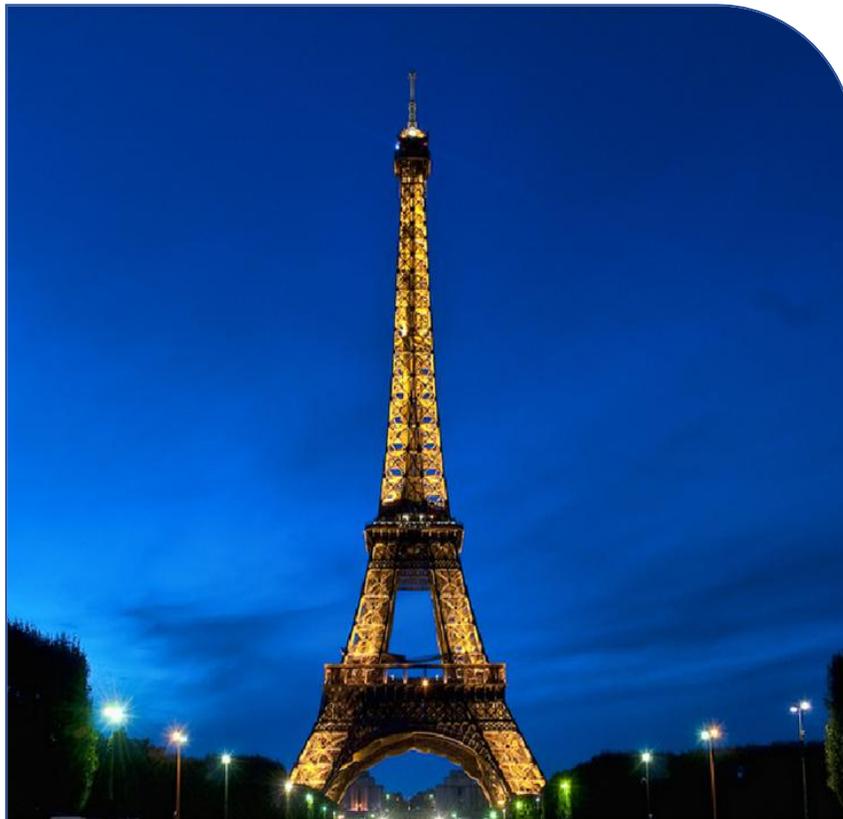


Merck Serono satellite symposium Controversial topics in ART: a conversation with the audience

14th World Congress on Controversies in Obstetrics, Gynecology
and Infertility

Paris, France
17–20 November 2011



This report presents highlights from a Merck Serono satellite symposium held in conjunction with the 14th World Congress on Controversies in Obstetrics, Gynaecology and Infertility. It is provided for information purposes only and does not represent the entire scope of the scientific content of the meeting. Any views or opinions expressed are those of the faculty and do not necessarily represent the opinion of Merck Serono or its associated entities. Merck Serono makes no representations of any kind about the completeness or accuracy of the information provided. Merck Serono is the financial supporter of the meeting and the production of this report, as part of an ongoing commitment to support scientific education for medical professionals.

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Introduction



The 14th World Congress on Controversies in Obstetrics, Gynecology and Infertility (COGI) took place from 17 to 20 November 2011 at the Pullman Paris Montparnasse in Paris, France. The COGI congresses are specifically designed to provide an opportunity to discuss controversial topics in obstetrics, gynaecology and infertility with an emphasis on clinical solutions in cases where no agreed-upon answers or consensus exists. The congress provides clinicians with insights and scientific take-home messages that can improve treatment and solve problems in the most difficult situations.

In conjunction with COGI 2011, the Merck Serono satellite symposium titled **Controversial topics in ART: a conversation with the audience** was held on 18 November. Professor Francois Olivennes, from the IVF Centre Eylau La Muette, Paris, France chaired the meeting and led a distinguished faculty in discussing some of the currently contentious issues in assisted reproductive technology (ART). Treatment discussions focused on gonadotrophin releasing hormone (GnRH) antagonist versus agonist use, methods and sources of progesterone supplementation, convenience and comfort of fertility treatments, predicting patient success per cycle of stimulation and customisation of controlled ovarian stimulation (COS). Professor Olivennes asked the audience several questions before each presentation to gauge their attitudes, opinions and current treatment practices. Additionally, some of the questions were repeated at the end of each presentation to assess any changes in audience opinion.

Utilisation of antagonists in normal responders: useful or not?



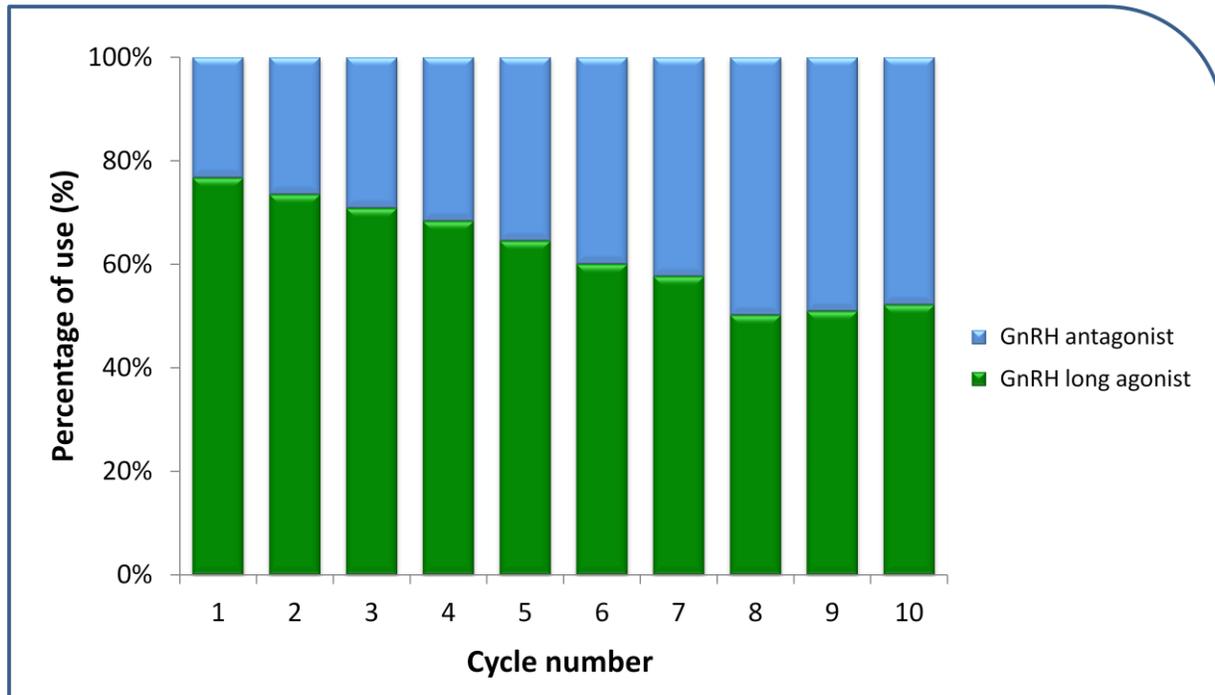
Georg Griesinger

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Data from the German National IVF registry

The use of GnRH antagonists in ovarian stimulation is controversial and the uptake of GnRH antagonists over the last decade has been slow. The latest figures supplied by the German National in vitro fertilisation (IVF) registry demonstrate that the long GnRH agonist protocol remains the most widely used treatment protocol in Germany today, with 43% of patients receiving long GnRH agonist versus 38% who receive GnRH antagonist. Analysis of clinical pregnancy rates (CPRs) in 2008 using the German IVF registry demonstrated little difference in the CPR per embryo transfer (ET) between different types of protocol (short GnRH agonist, long GnRH agonist, GnRH antagonist, no GnRH analogue), but that the CPR with long GnRH long was slightly higher. However, it should be noted that observational data such as that used in the German IVF registry can be biased by patient selection and should be treated with caution. Further analysis of 300,000 IVF cycles in the German IVF registry showed that although the long agonist cycle was the most common first cycle, patients who failed to become pregnant in their first cycle were more likely to receive antagonist in subsequent cycles. Additionally, the level of antagonist use further increased with repeated cycle failures (Figure 1). Interestingly, it appears that the majority of clinicians believe that antagonist protocols are most appropriate for patients who failed to become pregnant or older patients (36–55 years of age).¹ These patients are often less likely to become pregnant and therefore there is a danger that low pregnancy rates (PRs) may reinforce clinicians' beliefs that GnRH agonists should be used as a first choice in ovarian stimulation or in COS.

Figure 1: Agonist treatment failure and increased antagonist use in Germany¹



Observational data from registries such as the German National IVF registry can provide interesting findings, however, randomised controlled trials are required to determine if there are any differences in CPR or in PR between long GnRH agonists and GnRH antagonist protocols.

Systematic reviews and meta-analyses

Meta-analyses of studies comparing long GnRH agonists with GnRH antagonists show conflicting results for CPR, although the overall picture is that GnRH antagonists do not appear to be as effective as long GnRH agonists.²⁻⁶ This has stimulated ongoing debate and is likely to have influenced clinicians' attitudes towards GnRH antagonist use and could be responsible for the slow uptake of GnRH antagonists. Professor Griesinger highlighted that the meta-analyses that have been conducted to date all used PR as their primary endpoint. In the first Cochrane review of GnRH agonists versus antagonists by Al-Inany and colleagues in 2002³ and a second meta-analysis in 2006,⁵ results demonstrated a lower CPR with GnRH antagonists than agonists. However, a more recent analysis of the same studies showed no difference in the live-birth rate between treatment protocols.⁶ This new information and the availability of data from more trials (n = 7,511 women from 45 trials) has led the authors of the 2006 Cochrane review to revise their conclusions about the relative effectiveness of the two GnRH protocols. The authors now conclude that GnRH antagonists result in similar live-birth rates to GnRH agonists and that this, combined with a reduction in ovarian hyperstimulation,

justifies a move away from the standard GnRH agonist to GnRH antagonist protocols.⁷ All available meta-analyses agree that GnRH antagonists have a lower adverse effect profile than GnRH agonists with a risk reduction of approximately 50% for severe ovarian hyperstimulation syndrome (OHSS). Patients receiving GnRH antagonists also receive analogue treatment for a shorter period of time, have a shorter duration of ovarian stimulation and require fewer interventions to prevent OHSS than those treated with GnRH agonists.^{5,6} Additionally, contrary to popular opinion that GnRH antagonists are better for poor responders, recent meta-analyses have shown that there are no significant differences in poor responders in terms of the number of oocytes retrieved, CPR or ongoing PR between patients receiving GnRH antagonists and GnRH agonists.^{7,8}

Figure 2: Meta-analyses show that GnRH antagonists have a lower adverse effect profile than GnRH agonists^{5,6}

| | Al-Inany ⁵ | Kolibianakis ⁶ |
|--|--|--|
| Duration of analogue treatment | -20.90 days (95% CI: -22.20, -19.60) | -19.48 days (95% CI: -21.05, -17.91) |
| Duration of ovarian stimulation | -1.54 days (95% CI: -2.42, -0.66; p=0.0006) | -1.13 days (95% CI: -1.83, -0.44) |
| Risk of severe OHSS | OR 0.61 (95% CI: -0.42, 0.89; p=0.01) | RR 0.46* (95% CI: 0.26, 0.82; p=0.01) |
| Interventions to prevent OHSS | OR 0.44 (95% CI: 0.21, 0.93; p=0.03) | NR |

*For every 59 women treated with a GnRH agonist versus GnRH antagonist, 1 additional case of severe OHSS will occur.
CI = confidence interval; OR = odds ratio; RR = risk ratio; OHSS = ovarian hyperstimulation syndrome; NR = not reported

Changing opinions on GnRH antagonist use in Germany

Data from the German IVF registry have shown that attitudes toward the use of GnRH antagonists as first choice for ovarian stimulation are changing. The use of GnRH antagonists increased steadily from 21% to 31.5% to 38% in 2006, 2008 and 2010, respectively.

Questions to the audience

Before Professor Griesinger gave his presentation 81% of the audience stated that they already used GnRH antagonists in normal responders and 30% believed PRs were lower with GnRH antagonists. Whereas after the presentation, only 20% of the audience thought that PRs were lower with GnRH antagonists.

Summary

- There is no difference in live-birth rate between patients receiving GnRH agonist and GnRH antagonist stimulation.
- GnRH antagonists are associated with a reduced risk of OHSS compared with GnRH agonists.
- GnRH antagonists have a shorter treatment duration with fewer injections than GnRH agonists.

Evaluation of different systems for progesterone supplementation in ART: are all the sources the same?



Evangelos Papanikolau

Evangelos Papanikolau is Clinical Director of the Human Reproduction and Genetics Foundation in Thessaloniki, Greece. He obtained his PhD degree on blastocyst transfer from Vrije Universiteit Brussel, Brussels, Belgium in 2008 with Paul Devroey as his mentor. He has authored or co-authored more than 60 scientific articles.

In the normal human menstrual cycle, progesterone levels are very low during the follicular phase and do not start to increase until 1–2 days before ovulation. Following ovulation there is a steady rise in progesterone levels which plateau after 5–6 days and then fall 3–4 days before menstruation. In contrast to the normal cycle, the use of human chorionic gonadotrophin (hCG) during IVF leads to high levels of progesterone before ovulation or oocyte retrieval, with levels plateauing before a dramatic decrease in progesterone 8–10 days after oocyte retrieval.

Luteal phase support in IVF

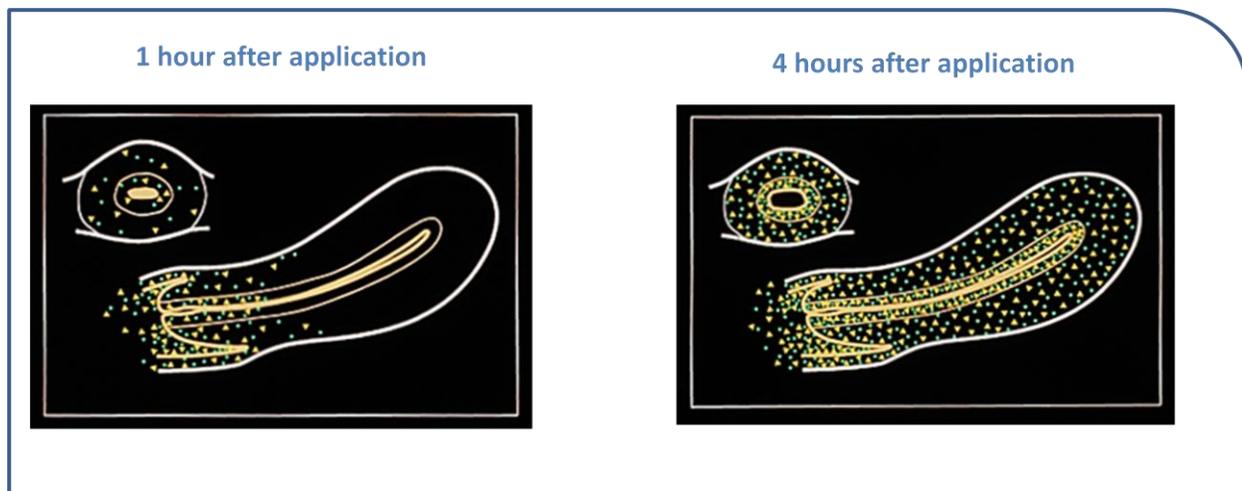
A meta-analysis of luteal phase support in randomised clinical trials was performed to determine the effect of progesterone on PR per cycle. Results indicated that although progesterone was not essential for pregnancy, patients who received progesterone were significantly more likely to become pregnant than patients who did not receive progesterone.⁹ Further to the meta-analysis, the American Society for Reproductive Medicine (ASRM) Practice Committee released a bulletin in 2008 observing that in IVF cycles down-regulated with a long-acting GnRH agonist, progesterone supplementation (50 mg/day administered intramuscularly [IM] or 200–600 mg/day administered vaginally) yields significantly higher pregnancy rates compared with treatment with placebo or no treatment.¹⁰

Routes of progesterone supplementation

Progesterone supplementation can be given via one of three routes of administration (oral, vaginal or IM), and is required in three situations; agonist protocol with hCG trigger, antagonist protocol with hCG trigger and antagonist protocol with agonist trigger. Oral progesterone has been shown to be ineffective with 90% of

the progesterone being degraded to its 5 α - and 5 β -reduced metabolites, leaving only 10% of the progesterone in the blood.¹¹ Additionally, Bourgain and Devroey reported the absence of any secretory transformation of the endometrium in patients treated with oral micronised progesterone compared with IM or vaginal micronised progesterone.^{12,13} In contrast, vaginal progesterone diffuses progressively over a 4-hour period after application from the cervix to the fundus of the uterus (Figure 3).¹⁴ Further studies have shown that serum progesterone levels are much higher following IM administration than vaginal administration; however, levels of progesterone in endometrial tissue following vaginal administration (Crinone[®] 8% vaginal progesterone gel) are double that of IM administration.¹⁵

Figure 3: Progressive diffusion of vaginally applied progesterone from the cervix to the fundus of the uterus¹⁴



A meta-analysis of GnRH agonist protocols using vaginal or IM progesterone demonstrated no difference in CPR or pregnancy loss between these administration routes.¹⁶ Investigations into CPRs using different delivery systems for vaginal progesterone have demonstrated that vaginal gels and vaginal capsules are equally as effective for achieving clinical pregnancy.¹⁷

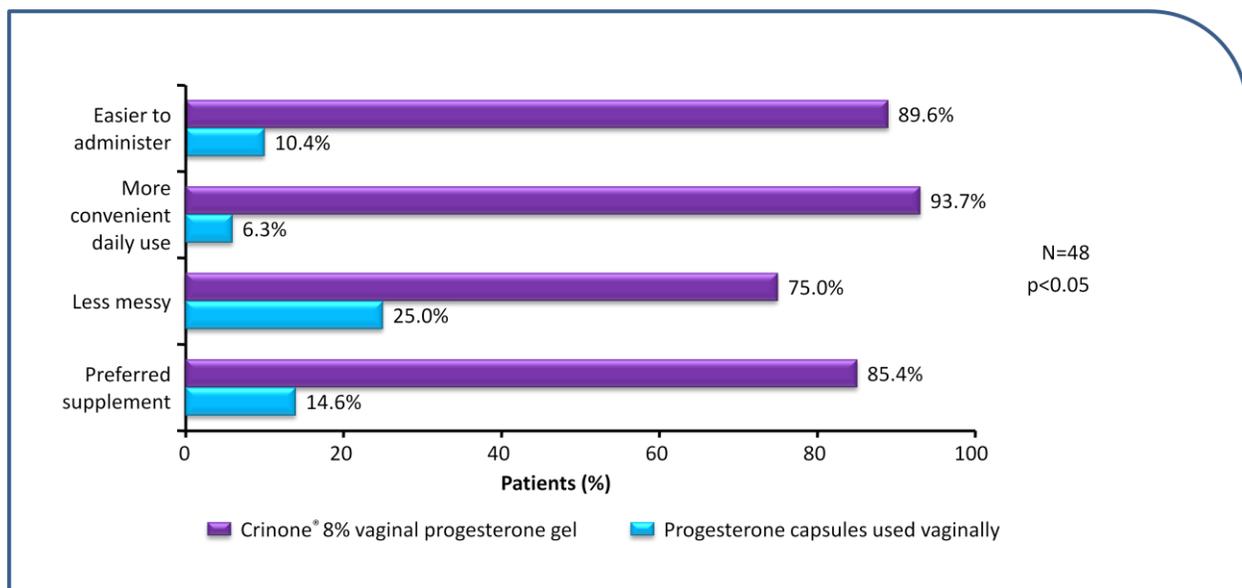
Timing of initiation of progesterone luteal support

The timing of initiation of progesterone luteal support has been investigated in GnRH agonist down-regulated IVF/ET cycles. Results showed no differences in CPR or in the number or quality of retrieved oocytes whether progesterone was started after hCG administration, on the day of oocyte retrieval or on the day of ET.¹⁸ Additionally, there were no significant differences in mean serum progesterone levels during the remainder of the luteal phase when progesterone was started after hCG administration, on the day of oocyte retrieval or on the day of ET.¹⁸

Patient satisfaction with route of progesterone administration

Patient satisfaction was shown to be higher with Crinone® 8% vaginal progesterone gel than with IM progesterone in a randomised controlled trial.¹⁹ The use of vaginal progesterone also avoids the formation of injection site abscesses that can be caused by the delivery of IM progesterone. When questioned in a separate survey, patients reported that Crinone® 8% vaginal progesterone gel was easier to administer, more convenient for daily usage, less messy and their preferred supplement compared with vaginal progesterone capsules (Figure 4).²⁰

Figure 4: Patient preference for Crinone® 8% vaginal progesterone gel versus vaginal progesterone capsules



Questions to the audience

Before Dr Papanikolau gave his presentation, the audience were asked several questions relating to their clinical use of progesterone and their beliefs on administration routes. Nearly all (97%) of the audience reported using progesterone supplementation, and of these, 3% used oral progesterone, 11% used IM progesterone and 86% used vaginal progesterone. Before listening to Dr Papanikolau's presentation, 11% of the audience thought that pregnancy rates were lower with vaginal versus IM progesterone; this number was 7% after the presentation.

Summary

- Progesterone supplementation in ART improves outcomes.
- Vaginal and IM progesterone are equally as effective for achieving clinical pregnancy.
- Patients prefer the vaginal route of progesterone administration to IM administration.
- The start date of progesterone administration (after hCG administration, on the day of oocyte retrieval or on the day of ET) does not appear to affect treatment outcome.

Defining the optimal number of oocytes and embryos produced to increase the cumulative chances of pregnancy: which is better, more or less?



Nicolás Garrido

Nicolás Garrido is Laboratory Director of the Andrology Laboratory and Semen Bank at the Instituto Valenciano de Infertilidad (IVI) in Valencia, Spain. His primary areas of research are molecular markers of male infertility and sperm survival after freezing/thawing, ART in HIV/VHC serodiscordant couples, and evaluation of ART results. Dr Garrido has published over 70 articles and 40 reviews or book chapters on fertility.

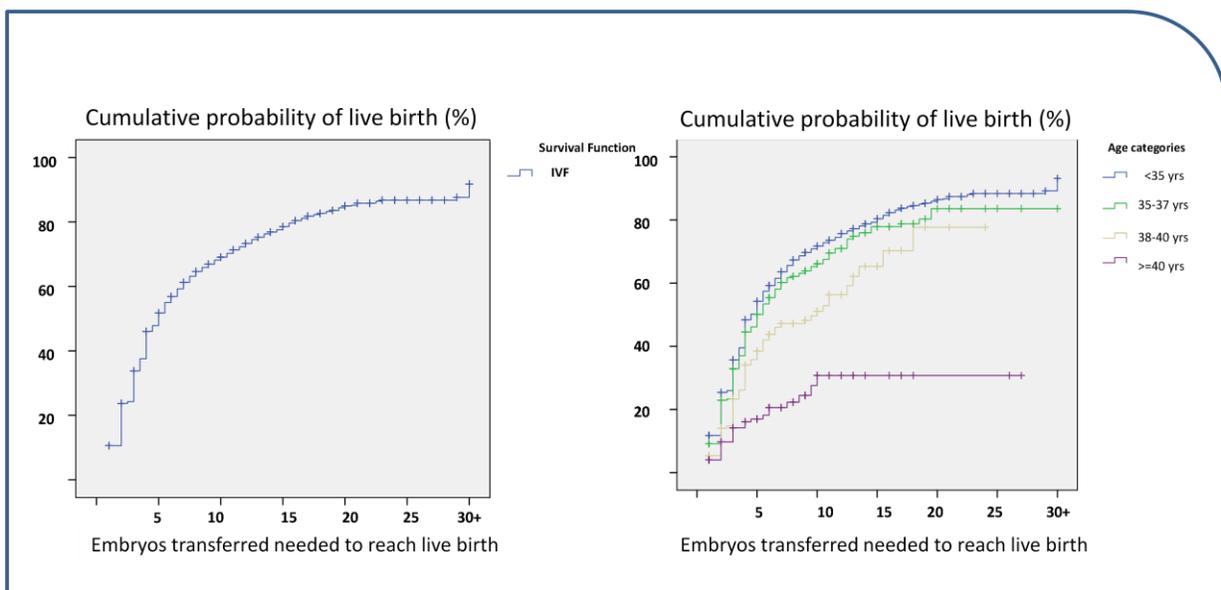
How do we measure IVF success in ART?

The main endpoint reported for success in ART should be the delivery of a healthy newborn, as this is the 'cure' for infertility. Currently, several endpoints are used to determine the success of IVF, including PR and ongoing PR. To enable accurate comparison between treatment protocols it is important to use standardised units for measuring success in IVF. In addition to differences in IVF success rates there are also differences in the definition of ART as a whole. Some clinicians consider ART to end after a single ET, others consider the end of ART to be after all of the embryos generated from a single COS (fresh and frozen) are transferred. It is also vital to have realistic expectations from ART and to know when to stop treatment, and in this respect the use of cumulative live-birth rates as a measure of IVF success would be very useful. Cumulative live-birth rates are measured using Kaplan-Meier estimation and represented by curves showing the probability of a live birth depending on time, opportunities to succeed or numbers of embryos/oocytes/treatments for couples at risk. Currently available studies in the literature estimating cumulative live-birth rates have limitations due to small sample sizes, inconsistent inclusion criteria and outcome measures, and do not include the transfer of frozen embryos or live-birth rates.²¹⁻²⁴ Theoretically, women who have more than one ET/cycle will have more chances of a live birth than patients who only have one ET/embryo, since after the same number of embryo transfers, they would have been in contact with more embryos.²⁴ A limitation to this approach is that the curve is a step function, with sudden changes in the estimated probability per cycle giving rise to survival curves with very low definition, thus complicating the interpretation of results. Further, current studies present data for up to six cycles only and the number of embryos replaced is not considered despite the relevance of this parameter in IVF success.

What is the cumulative live-birth rate per total number of embryos needed to reach newborn in consecutive IVF cycles?

A retrospective, single-centre, cohort analysis of cumulative live-birth rate per ovarian stimulation cycle to measure the success of IVF demonstrated that with embryos transferred in consecutive cycles, the chances of live birth significantly increase with each additional embryo up to 15 embryos (Figure 5). Further analysis showed that the probability of live birth reaches a plateau after the transfer of 25 embryos and increasing the number of embryos further does not improve the cumulative probability of live birth above this level. Further analyses demonstrated that live-birth rates are influenced by maternal age but not by infertility aetiology (Figure 5; IVI, Valencia, Spain).²⁵

Figure 5: Cumulative probability of live birth²⁵



Based on cumulative pregnancy rates a patient with donor oocytes requires fewer embryos to reach the same chance of live birth compared with IVF using the patient's own oocytes (10 versus 15, respectively).²⁵ As expected, the cumulative probability of live birth is not affected by recipient maternal age or aetiology.²⁵

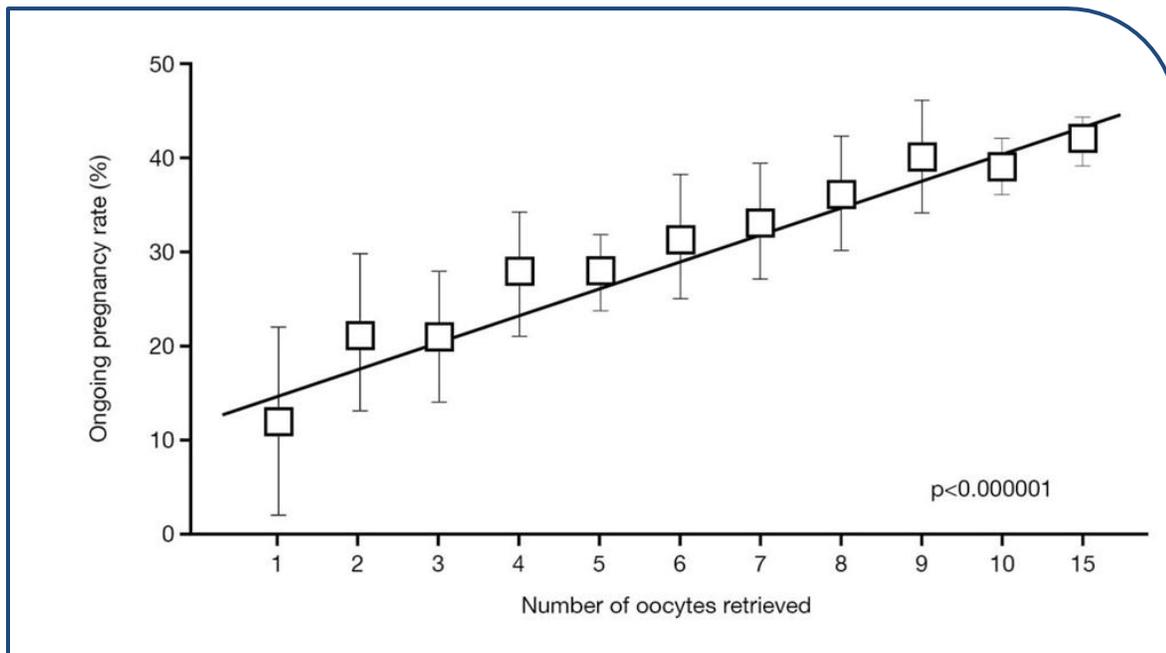
How many oocytes are required to have a live birth?

A common question is how many oocytes are required for a live birth? Unfortunately, there is no absolute answer to this question, but the likelihood per additional oocyte can be described based on a wide experience. Overall cumulative live-birth rates depend on the number of oocytes retrieved during IVF.

What is the optimum number of oocytes harvested in a single stimulation cycle?

The importance of achieving a good response to COS in terms of the number of oocytes was demonstrated by Bosch and colleagues, who published information on the relationship between the number of oocytes retrieved and ongoing PR (Figure 6).²⁶ Their data indicated that 15 oocytes should be harvested to provide the best ongoing PR.

Figure 6: Relationship between number of oocytes retrieved and ongoing pregnancy rate (IVI, Valencia, Spain; 2004–2008)²⁶



Further confirmation that 15 oocytes is the optimum number of oocytes that should be harvested per cycle to maximise the live-birth rate came from Sunkara and colleagues, who showed that retrieval of less than five or greater than 20 oocytes should be avoided during COS.²⁷ In summary, the higher the number of oocytes/embryos, the higher the levels of success as defined by cumulative live-birth rate. However, the oocytes should be obtained carefully during COS and retrieval of 15 oocytes per cycle is a reasonable goal to optimise the achievement of live birth.

Questions to the audience

Before Dr Garrido gave his presentation, 42% of the audience thought that 5–10 oocytes was the optimum number of oocytes to collect to increase the cumulative chances for live birth and 30% thought that 10–15

was the optimum number. After Dr Garrido's presentation, 10% of the audience thought that 5–10 oocytes was the optimum number and 51% now thought that 10–15 was the optimum number.

Summary

- Up to 15 oocytes, the higher the number of oocytes/embryos, the better the cumulative live-birth rate.
- Different patient subgroups have different plateau levels for cumulative live-birth rate.
- Fifteen oocytes appears to be the optimum number that should be retrieved in a single COS cycle with fresh transfer.
- Higher numbers of retrieved oocytes may not necessarily reflect higher levels of aneuploidy.

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Prepared 14 December 2011

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