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► To cite this version:

Paul Pirtea, Dominique de Ziegler, Marine Poulain, Jean Marc Ayoubi. Which key performance indicators are optimal to assess clinical management of assisted reproduction cycles?. *Fertility and Sterility*, 2020, 114, pp.24 - 30. <10.1016/j.fertnstert.2020.04.055>. <hal-03491544>

HAL Id: hal-03491544

<https://hal.science/hal-03491544v1>

Submitted on 15 Jul 2022

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Which KPIs are optimal to assess clinical management of ART cycles?

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Capsule

Clinical key performance indicators (KPIs) serve for monitoring the clinical factors pertinent to the quality and efficacy of ART activities.

Key words

Performance

Key performance indicator (KPI)

Clinical ART outcome

Sustained implantation

Summary

Like all industries, fertility clinics should identify and follow reference markers of its activity - Key performance indicators (KPI) - allowing ART outcome to be monitored and compared. Clinical KPIs revolve around following set parameters of the patient population, procedure and outcome data. Moreover, KPIs should also include identified protocols and standard operation procedures (SOP) followed in the daily practice and keep track of multiple pregnancy rates, a ruthless confounder of ART outcome.

Keywords

Infertility clinic

Assisted reproductive technologies (ART)

Performance

Key performance indicator (KPI)

Outcome

The need for Key Performance Indicators (KPI) in clinical ART

Three primary KPIs in clinical ART

Since inception, the results of ART have hovered between 0% and 100%. If ART pregnancy rates had remained around 0%, as it was the case in the very early days, the whole process would have been long forgotten. Conversely, if ART results would now regularly approximate 100%, we would not be talking much about it, as positive outcomes would be the rule for all ART attempts. It is because through its 40-year history ART results have been sizable, but yet clearly remain less than 100%, that all infertility clinics strive for constantly optimizing their care by improving processes and/or adding new measures. This constant drive for better results in ART is the base for the need to establish markers of outcome, known as key performance indicators (KPIs).

The imperfections of ART results may be due in part to shortcomings in the clinical treatments or laboratory processes. But beyond the technical issues – clinical or biological –, the less-than-100% outcome of ART also stems from the inherent limitations of human reproduction. Contrary to other human functions, such as, for example, digestion, for which 100% efficacy is expected, human reproduction does not work all the time even when conditions are optimal. Of 100 young couples trying to conceive, say 70 are bound to succeed within 3 months or so. As these couples conceived rapidly, they are naturally considered as perfectly normal reproduction wise. Yet not all these normal young women and men conceived during their first or even second month of trying. Hence, we see that it is normal for human reproduction to not work 100% of the time, contrary to reproductive conditions prevailing in other animal species, as say the rabbit. Logically, the natural limits of human reproduction apply in ART as well. While the latter can slightly outperform natural conception – through multiple ovulation and various ways of embryo selection – it remains however limited by the inherently poor efficacy of human reproduction.

When assessing ART results in a given center, we must therefore sort out what depends on the quality of the ART process – clinical and biological – from what is inherent to the limitations of human reproduction. These problematics underscore the need to identify markers or KPIs that allow to monitor the efficacy of ART in order to compare results between different centers and monitor the outcome of a given center over time. This monitoring process implies following the laboratory work and clinical steps of ART. The former is addressed in a sister publication of the present series (Fabozzi et al.), while clinical management of ART is discussed here. Practically therefore, monitoring clinical ART – i.e. defining KPIs – implies assessing three sets of parameters that define: (i) the patient population, (ii) various ART procedures and (iii) adequate ART outcome indices, as illustrated in Table 1.

Patients

The efficacy of ART greatly depends on the characteristics of the patient population being treated, such as, notably, the age of the female partner, duration of infertility and number of past ART attempts. Irrespective of the progresses accomplished by ART over time, its results – pregnancy rates (PR) and miscarriage rates – remain greatly affected by the age of the female partner (1, 2). We now know that the decrease in PR and increase in miscarriages, that becomes progressively preponderant after the age of 37 years, is mainly due to an increase in embryo aneuploidy rates (3, 4). On the contrary, donor egg ART has provided evidence that the uterine function does not decline with age (5). Recent data showed that if euploid embryos are rarer in older women (4), their implantation chances and miscarriage risks are being practically similar to those of younger women (6).

The number of prior ART attempts also impacts on further ART chances with decreased outcomes in women who suffered multiple prior failures, as past ART failures select out women who have persistently impaired ART outcome. Patients with recurrent pregnancy losses, previous IVF failures, and prior aneuploidy have a significantly higher, age-independent aneuploidy rate compared to patients without infertility (7).

The role of the male partner is more difficult to assess, notably since the advent of ICSI. While the effects of paternal age on ART outcome is questioned (8), it is admitted that extreme male factors, including surgical sperm, may adversely affect embryo euploidy rates but not the sustained implantation of such embryos (9).

The impact of the patient population characteristics on ART outcome is so important that KPIs aimed at assessing results ought to closely monitor the patient population. Indeed, subtle changes – i.e. different source of patient recruitment leading to differences in patients' age, etc. – might occur surreptitiously in an ART program and thereby, affect ART outcome. For these reasons some have advocated following the results – KPIs – of a reference population constituted of young women – under 37 years of age – undertaking their first or second ART attempt. Today, however, this is better replaced by following the outcome of euploid embryo transfers (10).

Procedure

The ART procedures encompass laboratory and clinical steps. As said, the laboratory process is addressed in a different article of this series (Fabozzi et al.). The clinical steps are essentially three, - ovarian stimulation (OS), oocyte retrieval and embryo transfer (ET).

The quantitative response to OS can be predicted to a certain extent from ovarian reserve parameters such as notably, the antral follicle count (AFC) scores and AMH levels (11). OS results are assessed by the number of follicles obtained, plasma E2 levels achieved and ultimately, the number of oocytes and mature or MII oocytes harvested. OS consists in artificially maintaining FSH levels elevated – at the inter-cycle FSH rise level – thereby, preventing the mid-follicular phase drop in FSH levels (12). The latter is the normal mechanism whereby a single dominant follicle is being selected for ovulation in the natural cycle. While the pathophysiology of OS is fairly well understood – preventing the mid-follicular drop in FSH (12) – the links between actual FSH levels – amounts of exogenous FSH administered – and the magnitude of the OS response remains controversial (13-15). The actual ‘tailoring’ of FSH dose according to patients’ parameters such as weight and AMH levels for example for maximizing outcome while curbing risks – notably, the ovarian hyperstimulation syndrome (OHSS) risk – sounded logical. Results, however, speak otherwise. In an RCT, the tailored approach did not effectively prevent severe OHSS, as two severe cases were encountered in the tailored group (16). Today, one greatly prefers preventing OHSS by avoiding hCG when triggering ovulation, using GnRH-a instead (16). Conversely, in a meta-analysis a standardized FSH dose of 150 IU/day has been claimed to be as efficient on ART outcome, as doses tailored to ovarian reserve testing (17). The authors of this meta-analysis concurred however that ovarian reserve testing facilitated to proceed to dose reductions in women with a predicted high response (17). Hence, while parameters of OS outcome – number of retrievals, MI and MII oocytes and day-5 blastulation rate – are also part of clinical KPIs, the actual gonadotropin doses used for OS do not need to be, as detailed in Table 1. Protocols and standard operation procedure (SOP) must however exist to guide the actual OS process selected in a given clinic, as discussed in a following section of this article.

The complications of OS are of two types, insufficient and excessive responses. Insufficient responses – less than 2-3 maturing follicles – lead to OS and oocyte retrieval cancellation, a parameter that needs to be reported in clinical KPIs. Interestingly, however, diminished ovarian response associated with oocyte retrievals represent a quantitative but not qualitative reduction in performance. Indeed, patients with reduced response to OS have similar blastulation, euploidy rates and LBR per euploid ET as age-matched controls with normal response to OS (18). If oocyte quality of women with poor response to OS is at par with age matched controls, it remains that the number of oocytes retrieved positively impact ART outcome and notably cumulative PRs (19) (20).

At the opposite, excessive response to OS can lead to a frank ART complication, OHSS. OHSS with ascites formation, hemoconcentration, risk of DVT and pre-renal kidney failure was one of the most dreadful complications of ART – at times fatal –, which in the past occurred in 1-4% of cases (21, 22). Our current understanding of the pathophysiology of OHSS and the role played by hCG allowed to practically

eradicate the risk of OHSS by triggering ovulation with GnRH-a instead of hCG and deferring ET (23) each time OHSS is feared. It remains that these two complications of OS – insufficient and excessive responses – ought to be reported in the KPIs that monitor the activity of a given ART center (**Table 1**).

The oocyte retrieval procedure is fairly standardized since the introduction – and rapid global adoption – of the transvaginal ultrasound guided oocyte retrieval (24). Meta-analysis failed to identify a superior mode of pain relief to cover the procedure. Thus, the choice is let to patients to choose between conscious sedation and analgesia, light anesthesia using propofol or local paracervical anesthesia based on preferences and/or availabilities in each given program (25). Fentanyl can also be used as levels measured in follicular fluid and found to cause no embryo toxicity (26).

Complications of oocyte retrieval can occur and ought to be monitored carefully and reported as part of KPIs (**Table 1**). The most common complication – >50% of cases requiring hospitalization – are pelvic hemorrhages. These are most commonly intraperitoneal – with an ovarian origin – but can at time be retroperitoneal in case of pelvic vessel injury (27). Levi-Setti et al. report an incidence of complication per oocyte retrieval of 0.4%, of which hemoperitoneum constituted the majority with an incidence of 0.23% (27). In this analysis, the experience of the surgeon – >250 retrievals for safest outcome – played a role in the risk of retrieval complication as well as the number of oocytes retrieved (27). Pelvic pain is a common complication of oocyte retrievals and is generally managed by minor pain killers. Other complications of oocyte retrievals include tubo-ovarian abscesses with ovarian endometriosis being a recognized predisposing factor (28). Rarer complications include ureteral injuries (29). As illustrated in **Table 1**, the incidence of retrieval complications ought to be part of clinical KPIs.

The efficacy of oocyte retrieval – number of oocytes retrieved per large follicles present – remains matter of controversies, with a likely impact of the doctor's experience (27). Data from meta-analysis suggest little or no difference between follicular flushing and simple direct aspiration with respect to oocyte yield, total embryo number, or number of cryopreserved embryos (30). In addition, follicular flushing probably makes little or no difference in the clinical pregnancy rate. Evidence was insufficient to allow any firm conclusions with respect to adverse events or safety (30). We do not support including the number of oocytes retrieved in relation to the expected retrieved as a routine KPI because of excessive variability. Other parameters of oocyte retrieval such as number of no oocyte retrieved, global MI and MII oocytes retrieved, fertilization and day 5 blastulation rate are part of followed KPIs, although these overlap with the laboratory KPIs, as addressed in a special article of this series.

As illustrated in **Table 1**, the third and last clinical procedure of ART is the embryo transfer (ET). ET, the last step of the ART process, should be most delicately conducted in order to avoid undoing all the

efforts put forth by the patient and clinical and biological teams together for optimizing results (31). This technical gesture requires also the most balanced hormonal environment. Recent data suggests that progesterone elevation ($P4 > 1.5 \text{ ng/dl}$) during the late follicular phase of ovarian stimulation for in vitro fertilization negatively impacts on ART-outcome, causing an advanced endometrial maturation and a direct negative effect on endometrial receptivity (32). This kind of situation requires cycle segmentation with freeze all-policy (33). Cancelling ET because of hormonal anomalies should be part of KPIs.

There is overwhelming evidence that ET ought to be performed under ultrasound guidance not just for efficacy sake (34) but also to allow all present in the room to witness the proper placement of the embryo and thereby lowering the stress level (35). Soft catheters are less traumatic and provide better outcome (36). KPIs ought to report the number of so-called difficult ET – taking twice the normal time –, which are known to adversely affect outcome (37). Likewise, KPIs ought to follow ET outcome for each doctor of the team on regular basis. Low performers ought to be informed and their technique reviewed until results become at par with others, taking the patient population characteristics into consideration.

Outcome

The ultimate outcome of ART is the live birth of a healthy baby. This should be kept in mind when assessing ART success rates with different metrics. The primary outcome parameters of ART are the sustained implantation (SIR), clinical pregnancy (cPR), ongoing pregnancy (oPR) and live birth rates (LBR), which all need to be part of clinical KPIs. All ART programs should compute SIR, cPR, oPR and LBR at time intervals – i.e. every 1-2 months – to assess quality of performance in relation to the number of OS initiated, oocyte retrievals and ETs. The difference between results calculated per OS initiated and oocyte retrieval represents the number of cancelled OS cycles generally for poor performance during OS or intercurrent events leading to OS cancellation. Generally, OS cancellation for poor performance affects 5-15% of cases depending on stringent OS criteria and/or population characteristics, OS cancellation being more frequent in older women and ART repeaters.

The advent of high-performance high-yield embryo cryopreservation through vitrification has led to an increasing number of cycles in which all embryos are cryopreserved and transfers deferred through what is called, segmented ART (38). The high incidence of freeze all and deferred ET forced us to monitor cumulative PRs (C-PR) and LBRs (C-LBR). For practicality sake, C-PR and C-LBR are computed as the number of pregnancies and live birth per ART procedure occurring within one year of the retrieval or until the first ongoing pregnancy is achieved (39).

For those segmented ART cycles, several protocols for LPS have been described, depending on what type of progesterone is available. In a recent article Devine et al. (40) reported higher early pregnancy losses when vaginal progesterone was used.

The PPO concept

As illustrated in **Table 1**, the clinical KPIs reflecting the (i) population, (ii) procedures and (iii) outcome (PPO) parameters of ART should be the primary parameters for following ART activity and judging efficacy. ART centers should follow and report these three sets – PPO – of KPIs for keeping track of possible changes in ART activity. Careful monitoring of the PPO parameters is the best recipe for starting trouble shooting in case of an unexpected decline in ART outcome.

Protocols and standard operation procedures (SOP) in clinical ART

ART activity is generally conducted within the scope of standard of care in the community for reproductive treatments. Furthermore, ART practice remains in compliance with existing guidelines edited by scientific societies, such as notably, the American Society of Reproductive Medicine (ASRM) (<https://www.asrm.org/news-and-publications/practice-committee-documents/>) and European Society of Human Reproduction (ESHRE) (<https://www.eshre.eu/Guidelines-and-Legal>). Within this context, ART activities are defined by two sets of rules, the protocols and standard operation procedures (SOP), which define each different step of the ART process, as illustrated in **Figure 1**. Protocols provide the group of rules that guide how an operation or sets of operations are being conducted. In other words, protocols give the context under which these actions are being performed. In ART for example, protocols governing OS procedures will define the type of synchronization (none, E2, OC pill) and mode of endogenous gonadotropin blockage long agonist or antagonist and in the latter case the mode of ovulation triggering hCG or GnRH-a. Procedures or SOPs on the other hand, define practically, in cooking recipe style, how each of the actions described in a clinical protocol is being conducted. A protocol is commonly associated with several SOPs describing the different procedures or choice of procedures undertaken in a given protocol. For example, a protocol will set the rules governing OS using an antagonist and say, synchronization with either E2, the OC pill or no synchronization measure at all. SOPs accompanying such protocol will spell out for example the various steps of procedures – the tasks to be done – like how oocyte retrieval are being conducted. Another related SOP will describe for example the possible use of the OC pill for the purpose of OS synchronization. The latter will detail the choice of OC pill retained, its onset mode in regularly cycling and non-cycling women and spell out the contraindications for using OC – and ways to identify them. Other SOPs will describe practically the monitoring of the ovarian response to OS, detailing how and when

follicular measurements are made on ultrasounds as well as the hormone measurements serving for OS monitoring.

Figure 1 depicts the sequence of protocols and related SOPs, warnings and consents, as they apply during the successive clinical steps of ART cycles. The various steps of the ART process – 1 to 8 – for which protocols and related SOPs apply are listed in Figure 1. KPIs should indicate whether protocols, SOPs, warnings and consent forms exist in a given ART clinic.

Quality control: the twin birth rate

In the hey days of ART, one way retained for improving the meager PR of the time was to proceed to multiple embryo transfers, a procedure that clearly increased both PR per transfer and multiple pregnancy rates. These days are over however, as we now have high sustained implantation rates (SIR) and access to highly effective means of cryopreservation by embryo vitrification and the possibility to only transfer euploid embryos through PGTA.

In a randomized non-inferiority trial, Forman et al. compared the outcome of single PGTA-tested single embryo transfer (SET) (n=89) vs. dual embryo transfer (DET) of untested embryos (n=86) (41). The oPRs in the SET and DET groups were comparable at 60.7% and 65.1%, respectively. The twin pregnancy rates were drastically different however, being at 0% and 53.4% for the SET PGTA-tested and DET groups, respectively (41). This prospective trial clearly indicates that SET of PGTA-tested embryos is as effective DET of untested embryos in terms of oPR per transfer, while eradicating the risk of twin pregnancy. The latest report of ART activity in the US (2016 activity) indicated that the global elective SET rate in women under 35 years of age was 42.7% (42). In 2016, ART contributed to 1.8% of all infants born in the United States and to 16.2% of all twins (42). With a twin pregnancy rate of 30% in the US, this resulted in 48% of all ART infants being twins, 62% of whom being delivered prematurely at an estimated cost of US\$1 billion annually (43). This is clearly unacceptable even if the outcome ART generated dizygotic twins is not different – maternal and neonatal – from naturally occurring twins (44).

In light of the impact of multiple pregnancy on children's health and cost to society, we must convene that DET is a ruthless mode of increasing PR for a clinic in days when a) cryopreservation through embryo vitrification allows to maintain cumulative PR (45) and b) SET PGTA-tested embryos provides similar PR as DET (41). It is thus necessary to include the twin pregnancy rates in the KPIs in order to assess and compare clinical performances of ART programs and serving as quality parameter of each fertility clinic. While a trend toward SET clearly exists, the ART generated twin pregnancy rate remains excessive. In the last ESHRE report available, the twin pregnancy rates varied in Europe from the upper twenties to 4.2% in both

Sweden and The Netherlands (46). As mentioned above the US clearly lag behind in this general effort toward electively practicing SET.

ART add-ons in fake news era

One of the primary preoccupation of couples wishing to undertake ART is to be informed on the success rates of clinics where they consider seeking treatment. In the US, over 95% of infertility clinics report their data to the society of reproductive technologies (SART - <https://www.sart.org>). Ultimately SART reports data from ART clinics annually, with the intention to provide information for the infertile population meant to help them make educated choices of their ART provider. Yet, due to several new technical issues notably, freeze all and deferred ET protocols, the interpretation of SART reports is most often too complex to guide patients in search for their ART clinic, as discussed in a separate article of this series (Fischer and Scott).

This fact that ART cycles are not always successful – irrespective of the efforts deployed – has led to the development of an endless list of add-on products and measures meant to improve ART success rates. These add-ons include various medications prescribed to one or both members of the couple with the intent to improve ART outcome, including through improving endometrial receptivity. The treatments and measures proposed generally have no or poorly validated bases, most often relying more on good thoughts and hypotheses – wishful thinking – than proven evidence for supporting their justification. These add-ons add cost – sometimes substantially – and are for the most part of unproven efficacy and sometimes even raise safety issues. Their use ought to be mentioned in the KPI list.

A recent series of Views and Reviews in Fertility and Sterility coordinated by Cynthia Farquhar dedicated to add-ons in ART pledged that we ought to be more honest in what is being prescribed (47). In this series, Kamath et al. list the clinical adjuncts most commonly used in ART (48). The authors particularly focused on dehydroepiandrosterone (DHEA), testosterone, growth hormone (GH), aspirin, heparin, antioxidants for the male partner and female partner, seminal plasma, and platelet rich plasma (PRP) intra-uterine infusion or intra ovarian injection (48). The observation that androgens increase the number of all categories of follicles in primates has served as basis for recommending their use in women particularly, those whose ovarian response to gonadotropin is insufficient. The use of DHEA at the dose of 75mg/day initiated 3 months before the onset of OS showed inconclusive results (48). The same is true for the use of testosterone administered in the form of gel or patches after excluding studies at high risk of biases (48). While intrauterine PRP administration, growth hormone and antioxidants prescribed to the male partner might have a beneficial effect, aspirin, seminal fluid administration at the time of the oocyte retrieval, heparin and antioxidants for the female partner do not show evidence of efficacy (48).

Sarah Lensen et al. report on ART adjuvants that are aimed at improving endometrial receptivity (49). These include immune therapies – corticosteroids, intravenous immunoglobulins (IVIg), granulocyte-colony stimulating factor (G-CSF), intralipids – endometrial scratching, endometrial receptivity array (ERA) and intrauterine human chorionic gonadotropins (49). These authors conclude that this series of add-ons aimed at improving endometrial receptivity lack robust evidence and should be only offered as part of clinical trials (49). Yet these endometrial targeted add-ons are like the above mentioned ART adjuncts commonly prescribed in infertility clinics at sometimes substantial cost for the patients – an ERA determination costs approximately US\$800 – despite the lack of strong supportive evidence. It is therefore necessary in an era when fake news easily snowball through the social media that clinics report the add-ons used – frequency, indication, etc. – in their list of KPIs reported.

Conclusion

KPIs are sets of parameters aimed at assessing the efficacy and safety of industrial processes, here the practice of ART clinics. The primary clinical KPIs reflect the 3 major parameters that are the patient population, procedures performed in ART and outcome parameters (PPO), as illustrated in **Table 1** and **Figure 1**. KPIs should also record the twin pregnancy rates – a risk factor – as multiple embryo transfer is a perverse way of improving pregnancy rates. Finally, clinical KPIs should also include the measures taken for establishing protocols, SOPs, warnings and consent forms, as well as indicating the different ART add-ons offered and their indications.

Table and Figure Legends

Table 1: The patient characteristics, procedure and outcome (PPO) parameters of KPIs in clinical ART

Figure 1: Protocols, SOPs, information, warnings and comments throughout the ART process

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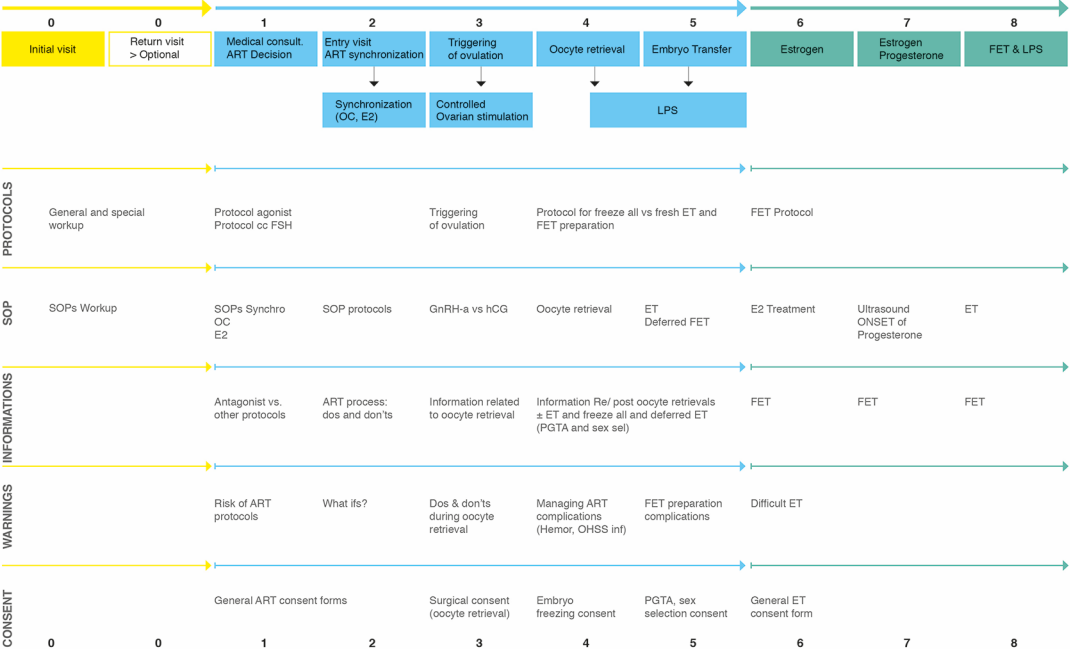
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INFERTILITY WORKUP

ART TREATMENT COURSE

FROZEN EMBRYO TRANSFER



	PATIENT CHARACTERISTICS	PROCEDURES	OUTCOME PARAMETERS
1	Female age <ul style="list-style-type: none"> • Age limit • Mean age • % <37 years old • % 37-40 years old • % >40 years old 	OS <ul style="list-style-type: none"> • % Cancelled retrieval • % Retrieval failure (no oocytes) • % OHSS 	Biological parameters <ul style="list-style-type: none"> • Nb oocytes, • MII oocytes rate • Fert rate • Day 5 blastulation rate • Thawing survival
2	Nb Poor ovarian reserve <ul style="list-style-type: none"> • Nb AMH <1ng/mL • Inferior AMH limit • Superior FSH limit • AFC inferior to limit 	Retrieval <ul style="list-style-type: none"> • % Hemorrhage • % Pelvic infection • % Other complication requiring hospitalization • % Oocytes retrieved/mature follicles 	Clinical Outcome <ul style="list-style-type: none"> • cPR, oPR, SIR • Miscarriage rate • LBR • C-LBR • Twin PR
3	Prior ART attempts <ul style="list-style-type: none"> • 	Embryo transfer <ul style="list-style-type: none"> • Retained embryos • Difficult transfers 	
4	Duration of infertility (mean) <ul style="list-style-type: none"> • 		
5	% Uterine factors <ul style="list-style-type: none"> • 		
6	% Nb Severe Male factor <ul style="list-style-type: none"> • 		
7	% Surgical sperm <ul style="list-style-type: none"> • 		