Cumulative live birth rate: time for a consensus?

Abha Maheshwari1,* , David McLernon2, and Siladitya Bhattacharya2

1Aberdeen Fertility Centre, NHS Grampian, Foresterhill, Aberdeen, UK 2Division of Applied Health Sciences, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB24 2ZD, UK

*Correspondence address. Aberdeen Fertility Centre, NHS Grampian, Foresterhill, Aberdeen AB25 2ZL, UK. Tel: +44-1224-438426; E-mail: abha.maheshwari@abdn.ac.uk

Submitted on August 2, 2015; resubmitted on September 13, 2015; accepted on September 24, 2015

ABSTRACT: Traditionally, IVF success rates have been reported in terms of live birth per fresh cycle or embryo transfer. With the increasing use of embryo freezing and thawing it is essential that we report not only outcomes following fresh but also those after frozen embryo transfer as a complete measure of success of an IVF treatment. Most people agree that an individual’s chance of having a baby following fresh and frozen embryo transfer should be described as cumulative live birth rate. However, views on the most appropriate parameters required to calculate such an outcome have been inconsistent. There is an additional dimension—time for all frozen embryos to be used up by a couple, which can influence the outcome. Given that cumulative live birth rate is generally perceived to be the preferred reporting system in IVF, it is time to have an international consensus on how this statistic is calculated, reported and interpreted by stakeholders across the world.

Key words: cumulative live birth rate / fresh embryo transfer / frozen embryo transfer / IVF, ICSI / pregnancy / life tables / embryo transfer

Background

The purpose of publishing data on the outcome of in vitro fertilization (IVF) is to provide stakeholders with information that addresses their specific needs. Clinicians need to be able to audit and evaluate care; consumers value a reliable way of understanding rates of success and complications while purchasers, regulators and politicians are interested in the demand for treatment, developments in service delivery and trends in clinical outcomes. For all, an ideal outcome is one, which provides a meaningful summary of the effectiveness of the treatment and its safety (Tiitinen et al., 2004).

Traditionally, the success of IVF has been reported on the basis of the outcome of a treatment initiated with the intention of replacing one or more fresh embryos by selecting the best embryo(s) for transfer within the uterus. Since the first live birth associated with a thawed frozen embryo was reported in 1984, freezing surplus embryos has become a feasible and increasingly popular option. With refinement of technology in recent years, the numbers of thawed frozen embryo transfers have increased (De Mouzon et al., 2010) as have pregnancy rates associated with them (Roque et al., 2013). This practice has been further encouraged by the strategy of single embryo transfer and an emphasis on preventing ovarian hyperstimulation in at-risk women. Reporting IVF success rates based on a fresh embryo transfer alone is meaningless in these situations and therefore outdated. The reporting of an IVF treatment should not only incorporate outcomes associated with fresh embryo transfers but also those resulting from the replacement of surplus frozen thawed embryos to provide an all-inclusive success rate which is comprehensive, relevant and meaningful. In this article we discuss how this can be reported, what the challenges are, and how these can be overcome.

Cumulative live birth rate: an all-inclusive success rate

Cumulative live birth rate (CLBR) has been suggested as a suitable way of reporting success of an IVF programme which incorporates fresh as well as thawed frozen embryo transfer (Germond et al., 2004). The term cumulative means increasing in quantity by successive additions. In the context of IVF it implies capturing the totality of live birth episodes following successive treatments. Conventionally, most IVF studies examine and report on the ‘per cycle’ or ‘per embryo transfer episode’ chance of pregnancy and delivery (Olivius et al., 2002). However, after an unsuccessful fresh cycle, couples often want to know what their chance is of having a live birth if they continue with further ART treatment—either utilizing any remaining frozen embryos accruing from their initial attempt or after further fresh treatments. Thus, from the patients’ perspective, the cumulative rate of live birth is more important (Malizia et al., 2013) since it better summarizes the chance of a live birth over an entire treatment period (Malizia et al., 2009) and is most pertinent to a couple’s decision on whether to undertake further IVF or not (Hull, 1994).

For clinicians, CLBR per oocyte retrieval is more meaningful as it is a much better indicator of quality and success in IVF in its totality as cryopreservation has become an integral part of IVF (Garrido et al., 2011;
It has been suggested that the outcome of a complete IVF cycle (including cryopreservation) allows better comparisons between different centres (Lintsen et al., 2010) which may possess different strategies for freezing and extended culture of embryos. Reporting CLBR rather than success rates based on fresh embryo transfer will be more appropriate for making economic and political decisions with regards to treatment efficacy and costs of reimbursement.

Despite these arguments, most national registries do not routinely report cumulative rates. This is due to a number of reasons as described below:

**Definition of cumulative live birth rate**

Defining cumulative birth rate itself is a major challenge. Computing rate of an event needs agreement about the most appropriate numerator and the denominator.

**Numerator for cumulative live birth rate**

Some studies have used first live birth (Thurin-Kjellberg et al., 2009; Luke et al., 2012; Stern et al., 2013; Bodri et al., 2014) as the preferred numerator while others have included all live birth episodes from an index stimulation cycle (Li et al., 2014). There are advantages and disadvantages of both approaches. Using the number of women who have at least one live birth as the numerator highlights the outcome for which couples initially sought treatment. However, as it is unable to capture the total benefit associated with a single egg collection, it cannot be used as a measure of ART efficiency.

There are no existing data to indicate what stakeholders prioritize as their final outcome—a single live birth or all live births from one egg collection. Preferences may also depend on their perspective—thus couples undergoing treatment, commissioners or clinics may differ in their choice. Using all live births as a numerator may give a rate of more than unity (e.g. 200%), which may not be intuitive or mathematically acceptable.

Choosing the right numerator is critical—not just in terms of communicating IVF results to patients and the public, but also in evaluating the efficacy of newly introduced treatments.

**Denominator for cumulative live birth rate**

The denominator could be all women who attempt ovarian stimulation as part of IVF or all those who have undergone egg collection. In addition, there is no consensus on how results should be interpreted for those who return for a repeat cycle of IVF after an initial live birth. In some studies these women were not re-enrolled in the data collection system after their first delivery (Bodri et al., 2014), while other researchers included them in any analysis as a ‘new patient under observation’ if they underwent further ART (Gnoth et al., 2011). Women who failed to return (either because they moved to another IVF centre or stopped treatment for any other reason) were censored after the last treatment (Gnoth et al., 2011). However, this makes the egg collection rather than the woman the unit of analysis.

There are two further components of the denominator:

1. **Unit of IVF treatment.**

   Assuming that the woman is the ideal denominator, it is important to determine the number of episodes of IVF treatment over which the cumulative live birth rate will be estimated. Some authors have suggested this should be all successive embryo transfers until live birth is achieved (Garrido et al., 2011) or only cycles which have cryopreserved embryos leading to fresh and some frozen embryo transfers (Bodri et al., 2014). Other studies assessed cumulative live birth rates over multiple fresh or frozen treatments which can be difficult to interpret. Much more intuitive is a policy of reporting cumulative rates over multiple complete cycles of treatment (where a complete cycle is defined as all fresh and frozen embryo transfers resulting from one episode of ovarian stimulation). However, this approach assumes that couples use up all their frozen embryos from previous egg collections before proceeding to the next egg collection, which may not be the case for all.

   Cumulative live birth rate can be reported over a course of a complete therapeutic episode but there is no universal agreement as to how many cycles of treatment constitute ‘complete therapy’ (Daya, 2005) and when ‘treatment’ is deemed to start and finish. It can vary from a single egg collection to any number of egg collections (Ke et al., 2013). The National Institute of Health & Care Excellence (NICE) defines ‘3 full cycles’ as 3 egg collections including all the fresh and frozen embryo transfers related to these. For a woman undergoing a number of egg collections, the cumulative live birth rate could be reported over multiple complete cycles of treatment (see Table I).

   The denominator here is per woman and it does not take account of drop off after first cycle. Moreover, this approach makes contemporaneous reporting of current or recent results impossible as one would have to wait till couples have completed a number of treatments. This will lead to presentation of results, which are outdated and unrepresentative of current practice, and therefore less relevant to most stakeholders, when presented at the end of three cycles.

   Reporting the number of cycles is of significance in situations where some centres perform multiple egg collections for a woman, create embryos and freeze them. Once a desired number of frozen embryos are available, they are thawed and the best quality ones are transferred. There are sometimes specific cases—such as women with suboptimal ovarian reserve in which patients would choose to undergo several potentially risky (ovarian stimulation and...

---

**Table I** How the conservative cumulative live birth rate is calculated over three complete cycles of IVF.

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>N2</td>
<td>N3</td>
</tr>
<tr>
<td>n1</td>
<td>n2</td>
<td>n3</td>
</tr>
<tr>
<td>n1/N1</td>
<td>n2/N2</td>
<td>n3/N3</td>
</tr>
<tr>
<td>(n1 + n2)/N1</td>
<td>(n1 + n2 + n3)/N1</td>
<td></td>
</tr>
</tbody>
</table>

N2 = N1 - n1 - w1,
N3 = N1 - n1 - n2 - w1 - w2,
w1 = the number of women who discontinued treatment without a live birth after cycle i.

Here, denominator = N1; numerator = number of women with at least one live birth; Cycle i includes all fresh and frozen embryo transfers resulting from the ith episode of ovarian stimulation.
Cumulative live birth

2705

egg collection) procedures in order to bank embryos prior to full utilization. In these cases, using live birth as a numerator but specifying the number of cycles it took to achieve this outcome will be informative. Another reason for specifying the number of cycles is that the precise protocol used may influence the number of stimulation episodes over a given period of time. Thus, a couple may receive more spontaneous (modified natural) cycles or antagonist cycles in comparison with long down-regulation cycles using GnRH agonists, which will impact on the overall outcomes.

(b) Time horizon.

Close linked with the number of treatments/cycles is the issue of the time horizon over which treatment is provided. There needs to be balance between contemporaneous data reporting and providing adequate time for couples to use their frozen embryos. Various methods have been advocated to take account of this. In some previous reports, women with frozen embryo(s) which have not been thawed by the end of an agreed follow-up period have been excluded from cumulative live birth analyses (Li et al., 2014). In others, conservative cumulative live birth rates have been calculated by dividing the number of women achieving live birth within a predetermined number of cycles, by the total number of women starting treatment. A third method estimates the cumulative live birth delivery rate after a specified number of cycles using a life-table analysis, by taking into account the effects of censoring (drop-out). The outcome measure associated with this method is referred to as ‘Expected cumulative delivery rate’ (De Brucker et al., 2009). These three methods cannot be compared directly as they are based on different assumptions.

Once we agree on the numerator and denominator, we need to specify the intended method of analysis.

Method of analysis

Life-table analysis has been used to estimate the success rates of various practices in the field of reproductive medicine including assisted reproduction (Hull et al., 1992). To use this method it is assumed that women who discontinue the treatment would have had similar chances of live birth as those who continue with further treatments—the independent censoring assumption (Stolwijk et al., 1996). However, some studies have found that women discontinue the treatment because of poor treatment prognosis, i.e. that the reason for censoring was not independent of the outcome (Doody, 1993; Walters, 1994). However, others (Haan et al., 1991) have not found any over-representation of patients with a poor prognosis in the group of dropouts.

Use of life table approach for multiple egg collections

The use of life table approach for multiple egg collections is associated with some limitations. In life table approach, used in this context, it is assumed that events are happening in consecutive menstrual cycles. Therefore, two women, each of whom have had three cycles of treatment, are considered similar for the purposes of comparison and data. However, in reality, there will be a difference in the time period during which each of them have these three full IVF cycles (i.e. fresh as well as linked frozen embryo transfer). There will also be a difference in the age at which second and third egg collections are performed in different women, even if first egg collection was done at the same age. This is due to the fact that length of time it takes to complete one full cycle of treatment will depend on the number of frozen embryos and the number of menstrual cycles required to transfer all these embryos. Moreover, women may have a gap between various episodes of embryo transfers for various reasons. It has been suggested (Engmann et al., 1999) that when calculating cumulative delivery rates by life-table analysis, the age of each woman should be recorded at the start of her first treatment cycle, even though this can cause an underestimation of age-related cumulative delivery rates. Another disadvantage of life-table analysis is that it also tends to overestimate the cumulative delivery rates when the group is too small (De Brucker et al., 2009).

Other model-based approaches can be used to estimate the probability of cumulative live birth in individual couples based on characteristics of the couple and their treatment (Missmer et al., 2011). These are beyond the scope of this discussion.

Discussion

Until agreement is reached on a consistent approach to reporting outcomes, it will be difficult to compare CLBR in ART across different studies or national registry reports. Some authors tend to publish three different outcomes: the conditional live birth rate at a specific cycle; a conservative estimate of the cumulative live birth rate, which was based on the assumption that none of the women who did not return for a subsequent cycle would have had a live birth; and an optimal estimate of the cumulative live birth rate, which was based on the assumption that women who did not return for a subsequent cycle would have had the same live birth rates as those who did return (Luke et al., 2012). This latter method represents an ideal world scenario where there are no barriers to treatment continuation. However, while helpful from a research perspective, this is unhelpful for comparing clinics and treatments by some stakeholders. Therefore, it is time to strive towards a consensus on a standard numerator, denominator (including unit of treatment and time horizon) and a method of analysis from the range that is available (Table II).

Preferences of stakeholders

Preferences of stakeholders on the best way of expressing cumulative IVF outcomes are not available in the literature. It may be that different groups have different perspectives and one definition may not be suitable for all. The suggested time horizon must be sensitive to the needs of couples undergoing treatment—an issue, which needs to be explored further.

Recommendations

To take account of the above factors and to avoid undue confusion we would recommend reporting of cumulative live birth rate over short-, medium- and long-term time horizons. Although, in the current electronic era, stakeholders could theoretically choose to view their preferred outcomes by means of drop down menus, such a laissez-faire approach towards data dissemination has the potential to complicate rather than simplify the process and lead to serious inconsistency in interpretation of results.

The most important requirement is to have a clearly defined numerator and denominator that clinicians/researchers must report alongside the outcome rate, as well as clarity around the statistical method used to
compute it. We may have to accept a three-step approach towards reporting cumulative live birth rate in the short, medium and long term.

**Short term.** To measure short-term outcomes, CLBR can be presented as live birth episodes per woman per egg collection over a 2-year period to account for the first live birth. A 2-year period is chosen as women are likely to use all their frozen embryos but unlikely to have two live birth episodes during this period.

**Medium term.** It is assumed that most, if not all, frozen embryos from a single egg collection will have been thawed and transferred within 5 years. To measure medium-term outcomes CLBR should be reported as live birth episodes per woman per one egg collection in a 5-year period. This will account for all live birth episodes (including second and further live birth) from one egg collection.

**Long term.** For long-term outcomes the CLBR could be reported as live birth episodes per woman per three egg collections over 10 years. Since the number of patients having three or more complete treatment cycles in each individual centre will be small, this will need to be reported at a national level to help policy makers make decisions about the number of cycles that should be supported by public funding. The assumption is made that most couples would have completed treatment within this time duration.

It is worth noting that this time based approach is based on number of egg collections and is unable to take into account the opportunities for conception (e.g. embryo transfers) over a given period. As cumulative live birth rates after 2, 5 or 10 years could be the same irrespective of the number of embryo replacements, this method of reporting cumulative outcomes will not be able to provide data on number of treatments needed to conceive or identify clinics where patients require fewer cycles to achieve a pregnancy leading to live birth.

Our suggestions, summarized in Table III relate to CLBR reporting only. We acknowledge that other relevant outcomes include measures, which determine the burden of treatment, risks of OHSS, patient experience and long-term safety for a woman and her baby. These are issues for consideration in order to capture a global view of the full impact of IVF treatment. The challenge lies in the practicality of achieving this—both in terms of tools and definitions used as well as the extended time horizon required for some of these. Clinics do not normally evaluate the patient experience and indeed, given that two individuals are involved, these experiences may be different for each of them. Long-term follow-up is ideal, but, as discussed earlier in the manuscript, truly meaningful long-term follow-up would mean reporting outcomes many years after treatment. While this is important, the two serve separate functions and cannot necessarily be combined in the same report and for the same purpose.

### Table III  Suggestions for reporting cumulative live birth rate.

<table>
<thead>
<tr>
<th>Suggested parameters</th>
<th>Account for</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short term</strong></td>
<td></td>
</tr>
<tr>
<td>Live birth episodes/woman/one egg collection in a 2-year period</td>
<td>First live birth</td>
</tr>
<tr>
<td><strong>Medium term</strong></td>
<td></td>
</tr>
<tr>
<td>Live birth episodes/woman/one egg collection in a 5-year period</td>
<td>All live birth episodes (including second and further live birth) from one egg collection</td>
</tr>
<tr>
<td><strong>Long term</strong></td>
<td></td>
</tr>
<tr>
<td>Live birth episodes per woman/3 egg collections over 10 years</td>
<td>All live births from 3 egg collections</td>
</tr>
</tbody>
</table>

### Conclusion

Patients beginning a course of IVF treatment need information about their chances of having a baby. This can be measured as the chance for live birth per treatment (fresh or frozen IVF) but it can also be presented as the likelihood of live birth following repeated treatments.

Although, it is possible to report on cumulative live birth rates, several different definitions are used. This makes it difficult to generate a single comprehensible headline figure, which captures the success rate of IVF/ICSI. Until agreement on this is achieved, we recommend a triple outcome strategy for reporting short-, medium- and long-term results.

### Authors’ roles

A.M. conceived the idea and wrote the initial draft. D.M. contributed to the manuscript, especially in terms of elaborating on the statistical concepts. S.B. contributed to the development of the initial concept and provided intellectual input in structuring the arguments in the text. All authors contributed to drafting and revising the manuscript. They all approved the final version.

### Funding

No external funding was obtained for this manuscript.
Conflict of interest

None declared.

References


Daya S. Life table (survival) analysis to generate cumulative pregnancy rates in assisted reproduction: are we overestimating our success rates? Hum Reprod 2005;20:1135–1143.


Li HW, Lee VC, Lau EY, Yeung WS, Ho PC, Ng EH. Cumulative live-birth rate in women with polycystic ovary syndrome or isolated polycystic ovaries undergoing in-vitro fertilisation treatment. J Assist Reprod Genet 2014;31:205–211.


