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ARTICLE

Follicle recruitment determines IVF productivity rate via the number of embryos frozen and subsequent transfers

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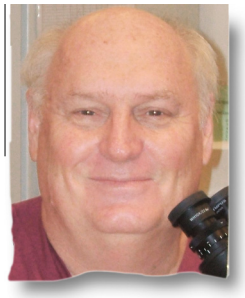

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Abstract IVF productivity rate is an index defined as the sum of all live births from either fresh or frozen embryo transfers arising from a single oocyte collection. This retrospective analysis over 9 continuous years used this index to understand the potential impact on pregnancy rates of milder stimulation regimens with associated reduced egg numbers. The productivity rate per collection increased in a linear and significant rate as more oocytes were recovered, more embryos frozen and more frozen embryo transfers contributed to pregnancy. This observation was true for women aged <35 years and less so for women aged 35–39 years but not for women aged 40 years and older. The contribution of frozen embryo transfer to the productivity rate rose in a linear manner, reaching over 40% of all live births with nine oocytes. The number of live births per oocyte, pronuclear embryos and thawed embryos decreased significantly but the number of live births per embryo transferred (fresh or frozen) rose with rising oocyte numbers, reflecting increasing opportunity for embryo selection. This study suggests that optimal benefits with minimal risks are gained from a model that includes both fresh and frozen transfers under stimulation generating between 8 and 12 eggs.

KEYWORDS: cumulative pregnancy rate, egg number, frozen embryo transfer modelling outcome, productivity rate

Introduction

The introduction of ovarian stimulation was initially seen as a positive advance increasing pregnancy rates and reducing the number of unsuccessful cycles by ensuring that one or more embryos were available for transfer. As technology improved, the rising multiple pregnancy rates have driven the transfer of fewer embryos such that currently many accreditation guidelines actively support single-embryo transfers. In some countries, this has encouraged the increased use of frozen embryo transfers to supplement the initial fresh transfers. In addition to improvements in

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laboratory standards, better pharmaceutical preparations have also seen increases in oocyte numbers and quality such that excessive responses to stimulation leading to ovarian hyperstimulation syndrome (OHSS) are also viewed as unacceptable. There have been several responses to avoiding OHSS. These include the promotion of 'minimal stimulation' (Fauser et al., 1999; Kato and Teramoto, 2007; Olivennes et al., 2009) or 'individualized stimulation' regimens to avoid OHSS (Fiedler and Ezcurra, 2012). In both models, the number of oocytes recovered is lower and as a consequence, the chance of live birth per initiated treatment cycle appears significantly reduced. Patient-defined stimulation regimens using anti-Müllerian hormone, antral follicle count and day-2 FSH such as the PIVET algorithm (Yovich et al., 2012) have also been proposed with a view to capturing the benefits of milder stimulation for a targeted subgroup.

Unfortunately, the promotion of minimal stimulation models has occurred in the absence of understanding the contribution of frozen embryos to the total productivity of each stimulation cycle. One reason why this has occurred is that clinicians, patients and accreditation bodies view fresh and frozen transfers as independent events (de Mouzon et al., 2012) when in fact the two have an entirely dependent relationship. An example of this is expressed by the annual national review of Australian clinics which only considers IVF from fresh transfers and bundles freeze-all cycles as frozen transfers (Sullivan et al., 2010). Concerns of the health of children from stimulation cycles may force the future linking of the collection cycle to frozen transfers with proposals to cryopreserve the higher-grade embryos or, indeed all embryos, for future frozen embryo transfer to optimize outcome (Healy et al., 2010). In reality, all the cost of a cycle is borne by the patient and the clinic during the initial collection cycle. The commitment of time and financial burdens by the patient, the allocation of staff and resources by the clinic and the cost of pharmaceutical and medical costs are all raised and committed during the collection cycle. In contrast, frozen embryo transfer (FET) cycles are relatively uncomplicated and inexpensive to both patient and staff. There is, however, only one cohort of oocytes created per stimulation cycle and their number, along with the quality of resultant embryos, will then define how many transfers may occur. Separating fresh and frozen transfers as independent events is misleading since the quality of the frozen embryos will be dependent on the stimulation protocol and the woman's response. A better way to view a cycle is not as a series of independent events but as a series of related and dependent events expressed as the number of live births per collection regardless of which transfer they arose from. This denotes the total productivity rate per cycle, a term introduced in an earlier study on growth hormone supplementation (Yovich and Stanger, 2010, p. 40) and avoids confusion with the cumulative pregnancy rate (CPR), which is a result of repetitive stimulation and/or transfer cycles. In reality, this is how patients view treatment. 'What is my chance of falling pregnant from this egg collection procedure?' has more meaning when viewed from a total productive perspective. This philosophy has assisted patients to accept the proposal of single-embryo transfers when they are seen to be inexpensive, simple extensions of the main treatment cycle.

Productivity rate, therefore, is a measure of the stimulation process itself since the number and quality of follicles and oocytes must dictate the eventual productivity. While varying the transfer day or number of embryos transferred may influence the fresh pregnancy rate, they may also influence the number of embryos frozen and indirectly the productivity rate, yet this is rarely examined. Applying a productivity rate model to a collection cycle provides a tool to examine all aspects of management including stimulation, embryology, embryo transfers and FET under one process. It is in this light that productivity rate has been used to explore the impact of oocyte numbers on the chance of pregnancy from a single collection cycle when many or all the embryos have been used or discarded. Since frozen embryos may remain in storage for many years and indeed are often used for a second chance of pregnancy, the application of productivity rate needs to be retrospective in nature. In this study, a consecutive 9-year period was used that provided at least a 1-year window post collection. The aim was to explore the impact of oocyte numbers on the productivity rate to provide a background reference for current modification of stimulation regimens specifically aimed at reducing oocyte numbers to avoid OHSS (Yovich et al., 2012) and to explore whether an optimal number of oocytes could be derived from the study as a basis for individualizing patient stimulation regimens.

Materials and methods

Data for all IVF treatment cycles at PIVET Medical Centre between 2003 and 2011 were included in the study except for oocyte donation patients and cycles where no oocytes were recovered. No cycles were excluded due to age or patient history and therefore are representative of most IVF clinics. The data presented has not been partitioned by age (except for one table detailing the productivity rate by age) since the aim was to present a global view of the interaction between oocyte numbers and outcome. The data for cases with more than 20 oocytes is presented in all figures as a pooled data set (18 cases where >20 were recovered), mainly due to the variability in the number of cycles and live births for each oocyte cohort but the linear regression analysis treated oocyte numbers as a continuous variable. Live births were the only outcome considered in the report. Clinical pregnancies and miscarriages were not considered.

All cycles covering both fresh and frozen embryo transfers were recorded on the PIVET Database using Filemaker Pro database that contained records from 2002 and internal purpose-developed software. All data was recovered using a standardized reporting module that includes information of both fresh treatment cycles and any subsequent FET cycles that arose from that oocyte collection.

During the 9-year period, follicle stimulation, oocyte recovery and transfer as well as embryo culture systems remained relatively stable and have been described elsewhere (Yovich and Stanger, 2010; Yovich et al., 2012) along with the cryopreservation methodology (Stanger et al., 2012). The details of patient demographics and cycle management are provided in **Table 1**. There were some changes in patient management over this period and the impact of these changes on the productivity rate was assessed using

Table 1 Population and stimulation characteristics.

Characteristic	*Aspirations (n = 3818)*
Age (years)	
<35	1595
35–39	1374
≥40	849
Insemination method	
IVF	861
Intracytoplasmic sperm injection	2957
Cycles	
Fresh transfer	3397
Fresh transfer and freezing	2015
No fertilization	187
Freeze-all cycles	234
Type of infertility	
Tubal infertility	1546
Endometriosis	639
Male infertility	2050
Unexplained	1193
Other/no reason	1140
Source of spermatozoa	
Donor	279
Husband sample	3489
Surgical	50
Protocol	
Long down-regulation	1048
Agonist (flare)	1454
Antagonist	1156
AACEP	136
Low-dose stimulation (including clomiphene citrate)	24
Fresh transfers	
Embryos transferred	
1 embryo	1979
2 embryos	1375
>2 embryos	43
Day of transfer	
1	12
2	262
3	2471
4	21
5	611
6	20

logistic regression analysis. Essentially, there was a drift from long down-regulation and agonist flare to antagonist regimens as were changes towards single-embryo transfer, blastocyst transfers and vitrification. The data was partitioned by age: <35 years, 35–39 years and ≥40 years, as has been reported elsewhere (Yovich and Stanger, 2010). Otherwise all data analysis comprised all patients regardless of age. This work also allocated FET to the egg collection of the transferred embryos even though in <1% of cases, the embryos were derived from more than one collection.

Definitions

Productivity rate is the sum of live babies delivered per trans-vaginal oocyte aspiration (TVOA). This included all single and multiple deliveries where each baby was counted as a live birth over the number of egg collections for a specific oocyte cohort. Birth rate per fresh transfer is the sum of all live births (singleton and multiple pregnancies) arising from fresh transfer over the number of fresh transfers for a specific oocyte cohort. Birth rate per frozen transfer is the sum of all live births (singleton and multiple pregnancies) arising from frozen embryo transfers over the number of frozen embryo transfers for a specific oocyte cohort.

Statistical analysis

The relationship between the productivity rate and oocytes collected was analysed by standard linear regression analysis and included all cases. In this data set, the maximum number of oocytes recovered was 40. Logistic regression was employed to develop a prediction model over all oocyte cohorts where the comparison was between no live births (value = 0) and one or more live births (value = 1) per collection; however, because of the negative impacts of the cycles with over 20 oocytes and given these were rare, extreme and clinically atypical recoveries, the logistic regression models presented were limited to cycles with 20 oocytes or less. The difference between the productivity rate and live birth per fresh transfer was made using Pearsons chi-squared analysis with Yates correction. Comparison of the number of thaws between successful and unsuccessful cycles was made using the variance ratio (F-test), a model to predict the number of live births per collection made using multiple regression analysis. The relationship between live birth rate and oocyte, embryos and transferred embryos was made using standard regression analysis. All calculations were performed using MedCalc software (www.medcalc.org).

Ethical considerations

This study was performed under Curtin University ethics approval no. RD_25-10 general approval for retrospective data analysis 2011. PIVET Medical Centre functions under national accreditation requirements (Reproductive Technology Accreditation Committee) as well as specific licensing under state legislation (Western Australian Human Reproductive Technology Act, 1991).

Results

In all, 3818 TVOA cycles were included in the study. The study period represented considerable change in cycle

management. The demographic characteristics are presented in **Table 1**. The mean oocyte number was 9.3 ± 6.1 and as expected was significant for skewness and kurtosis ($P < 0.001$). The mean number of live births per collection was 0.36 (**Table 2**) and the mean number of live births per delivery was 1.11. In other words, a third of all collections over the whole age and infertility history resulted in at least one live birth, of which 89% were a singleton outcome. Partitioned by age, the live births per collection was 0.59 for women aged <35, 0.43 for women aged 35–39 and 0.14 for women aged ≥40 years. This was higher than the live births per fresh embryo transfer, which was 0.36 (<35 years), 0.24 (35–39 years) and 0.09 (≥40 years). In all, there were 159 multiple pregnancies of which 14 were high-order deliveries, all of which occurred prior to the widespread introduction of single-embryo transfers.

Overall, the productivity rate was significantly related to oocyte numbers ($r^2 = 0.84$, $P < 0.001$) and significantly higher than both live births per fresh and live births per frozen embryo transfer above 7 oocytes. The productivity rate was similarly related to the number of embryos, number of frozen embryos and the number of FET cycles. Both live birth rates were significantly linked to oocyte numbers ($P = 0.002$ and $P < 0.001$, respectively), presumably due to increased selection capability. These changes were modest in contrast to the productivity rate where the rise was linear (**Figure 1**). This has more merit considering the productivity rate also included cycles with no fertilization or with deferred transfers (freeze-all cycles). The productivity rate therefore reflects the true outcomes from an egg collection rather than that reflected only by embryo transfer.

When partitioned by age, the productivity rate was also highly correlated with oocyte numbers for women aged <35 years ($r^2 = 0.67$, $P < 0.001$) and women aged 35–39 years ($r^2 = 0.28$, $P < 0.01$) but there was no correlation with egg numbers for women aged ≥40 ($r^2 = 0.01$; **Figure 2**). The productivity rate were similar between the younger and the middle age groups, with the recovery of 10 oocytes or less but thereafter the productivity rate rose to 60–80% for women aged <35: that is, for younger women with 10 eggs or more, the chance of at least one live birth exceeded 60% from either a fresh or frozen transfer and these were achieved with 1 or 2 embryos for every transfer (usually 1) and most likely to be a singleton delivery. Unfortunately, in this study, productivity rates for women aged ≥40 did not increase in a linear manner with rising oocyte numbers. Rather the rate rose slowly to about 20% but after 13 oocytes it declined. There were few pregnancies in this cohort of women ≥40 years from which 16 or more eggs were recovered.

A better understanding of the role of FET cycles on the productivity rate was obtained by examining the contribution of FET live births to the total live births per collection (**Table 2** and **Figure 3**). The proportion of FET-derived live births increased in a linear manner with oocyte numbers ($P < 0.001$) appearing to plateau at 10–15 oocytes and thereafter increasing dramatically as more freeze-all outcomes occurred. FET conception contributed to less than

Table 2 Number of live births per fresh embryo transfer, frozen embryo transfer and egg collection.

No. of oocytes collected	*Fresh transfer*			*Frozen embryo transfer*			*Egg collection*		
	Live birth	*Transfer*	*Live birth rate*	*Live birth*	*Transfers*	*Live birth rate*	*Live birth*	*Collections*	*Live birth rate*
1	13	106	12.3	0	3	0.0	13	153	8.5
2	16	145	11.0	1	10	10.0	17	189	9.0
3	43	206	20.9	4	29	13.8	47	233	20.2
4	52	266	19.5	9	72	12.5	61	290	21.0
5	67	312	21.5	16	104	15.4	83	326	25.5
6	80	267	30.0	15	107	14.0	95	275	34.5
7	64	258	24.8	22	136	16.2	86	276	31.2
8	66	249	26.5	33	174	19.0	99	259	38.2
9	50	215	23.3	34	144	23.6	84	221	38.0
10	47	188	25.0	34	151	22.5	81	197	41.1
11	63	207	30.4	42	170	24.7	105	213	49.3
12	62	202	30.7	31	174	17.8	93	210	44.3
13	46	155	29.7	31	127	24.4	77	163	47.2
14	52	136	38.2	33	144	22.9	85	146	58.2
15	41	131	31.3	30	130	23.1	71	136	52.2
16	24	89	27.0	35	99	35.4	59	97	60.8
17	16	73	21.9	31	91	34.1	47	79	59.5
18	13	59	22.0	20	79	25.3	33	67	49.3
19	13	34	38.2	7	42	16.7	20	40	50.0
20	7	25	28.0	13	56	23.2	20	37	54.1
22–40	18	74	24.3	104	431	24.1	122	211	57.8
Total	853	3397	25.1	545	2473	22.0	1398	3818	36.6

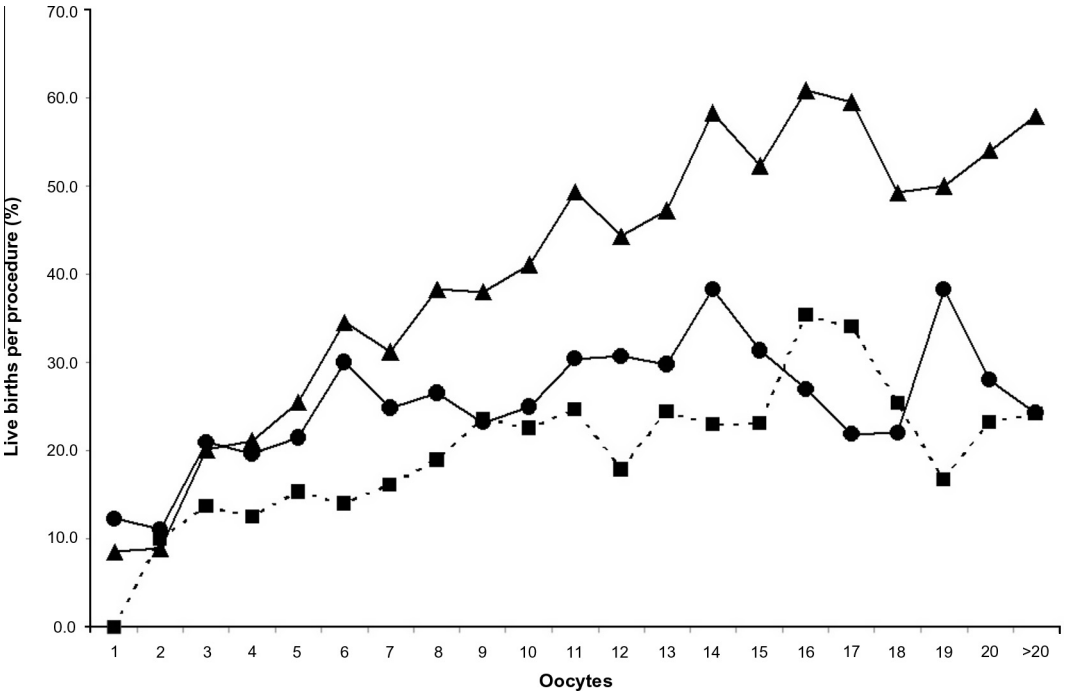

Figure 1 Live birth rates per fresh (●) and frozen embryo transfer (■) and per egg collection (▲) as a function of the number of oocytes recovered.

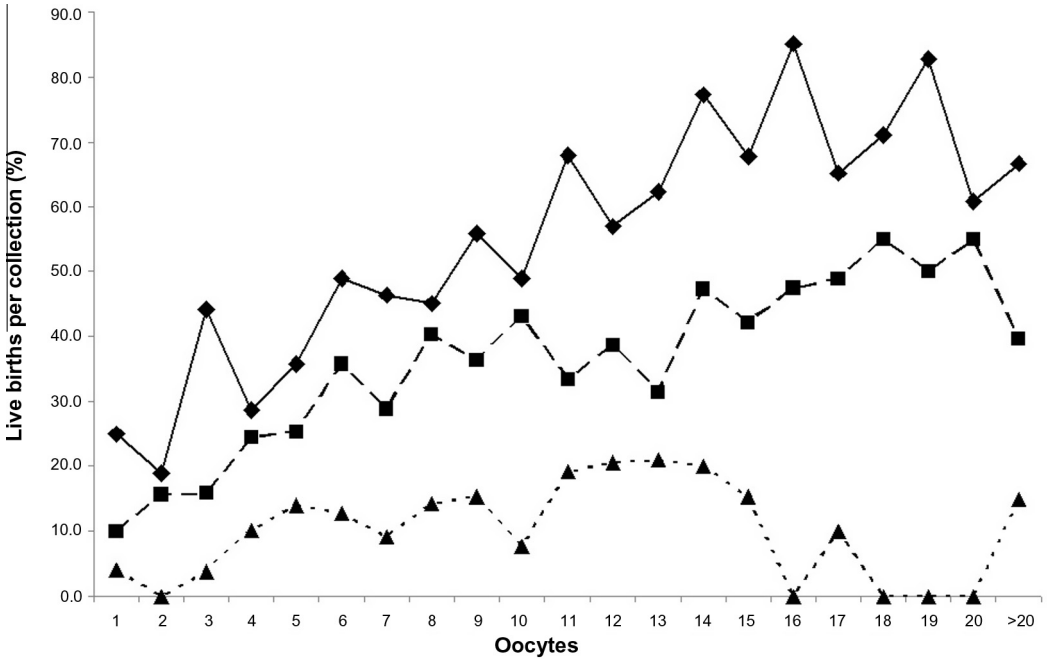

Figure 2 Live birth rate per egg collection by age group (♦, <35; ■, 35–39; ▲, ≥40 years) is shown as a function of the number of oocytes recovered.

20% of live births with six or less oocytes. The insert in Figure 3 identifies the significant relationship between the mean number of FET cycles per collection by oocyte cohort ($P < 0.001$).

The standard embryology parameters did not demonstrate any significant relationship to oocyte yields with the proportion of mature oocytes (oocytes with 1 polar body prior to intracytoplasmic sperm injection) and the fertilization rate (2-pronuclear embryos per oocyte). The proportion of usable embryos (suitable for either transfer or freezing/pronuclear embryos) was related to oocyte numbers ($P < 0.01$) most likely reflecting the influence of younger age and higher recovery rates.

In contrast, when the live births per number of oocytes or embryos transferred were used as key performance indicators, births per embryo and oocyte decreased significantly

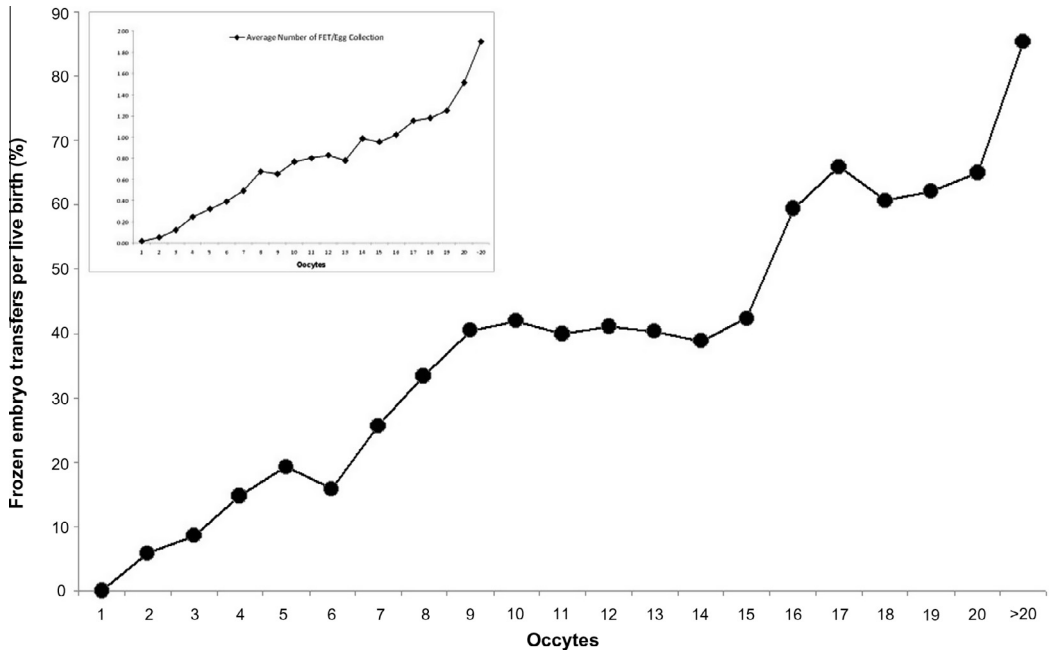

Figure 3 Influence of oocyte numbers on the contribution of frozen embryo transfers to the overall live birth rate as a function of the number of oocytes recovered in the original collection cycle. When 19—20 oocytes were recovered, more than 60% of all live births were derived from frozen embryo transfers. The insert graph shows the mean number of frozen embryo transfers per collection as a function of oocytes recovered. On average, there was 0.8 frozen embryo transfers per collection of 9—15 oocytes.

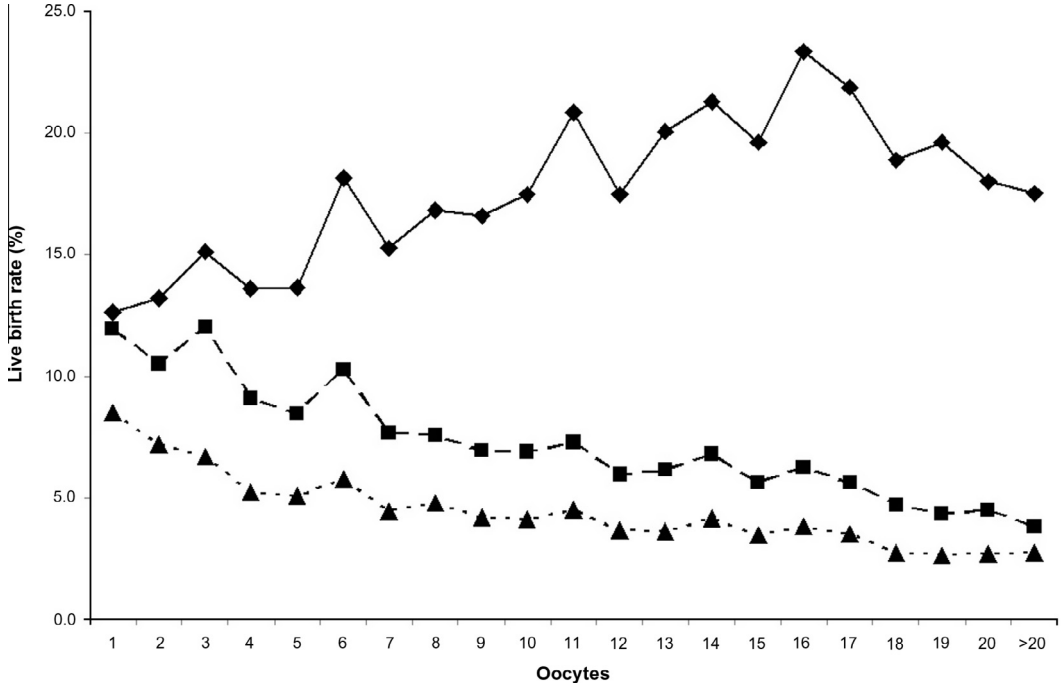

Figure 4 Proportion of live births as a function of the number of oocytes recovered in the original collection cycle (▲), the number of embryos created (■) and the number of frozen embryos transferred (♦).

with increased oocyte recovery (both $P < 0.001$) while live births per embryo transferred significantly increased ($P < 0.001$; **Figure 4**). It would appear that as oocyte numbers rose, an increasing number of embryos was used to select those suitable for transfer and that as more embryos were available, this selection became stricter. This is supported by the observation either that with larger oocyte numbers, fewer thawed embryos were suitable for transfer or that greater selection criteria were used to select those suitable for transfer (**Figure 5**).

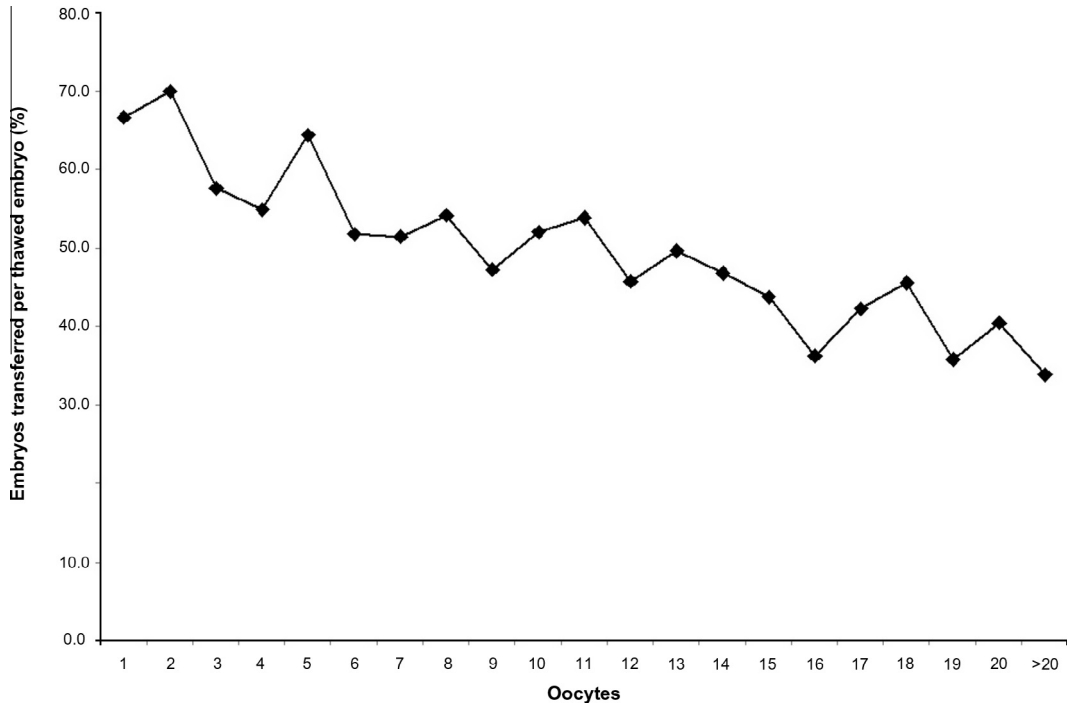

Figure 5 Proportion of frozen embryos actually transferred per thawed embryo as a function of the number of oocytes collected. The decrease in utilization of frozen embryos may reflect decreased viability or increased embryo selection.

Table 3 Logistic regression models of cycles with ≤20 oocytes predicting the likelihood of at least one live birth per egg collection.

Variable	*Coefficient*	P-*value*
Simple model		
Age	−0.1173 ± 0.0079	<0.0001
Oocytes	0.0528 ± 0.0006	<0.0001
Thaws	0.0947 ± 0.0412	0.0215
Constant	2.7521	
P-value stepwise method	<0.0001	
Complex model		
Age	−0.1074 ± 0.0008	<0.0001
Oocytes	−0.0307 ± 0.0142	0.0306
Thaws	−0.2703 ± 0.0563	<0.0001
Attempts	−0.0847 ± 0.0256	0.0009
Pronuclear embryos	0.0873 ± 0.0235	0.0002
Embryos frozen	0.2531 ± 0.0275	<0.0001
Constant	2.6474	
P-value stepwise method	<0.0001	

Variables not included in model: day of fresh transfer, number of embryos transferred, insemination method, stimulation protocol.

This study applied logistic regression analysis to the data using a simple limited variable stepwise model (Table 3) and an expanded multivariable model. In the simple model, age ($P < 0.0001$), oocytes ($P < 0.0001$) and the number of thaws ($P = 0.0215$) significantly predicted the likelihood of at least one live birth per egg collection. Expanding the variable list to include many of the parameters that may influence the chance of pregnancy, age ($P < 0.0001$), attempt number ($P = 0.0009$), oocytes ($P = 0.0306$) and thaw number ($P < 0.0001$) negatively influenced the outcome while the number of embryos ($P = 0.0002$) and the number frozen ($P < 0.0001$) significantly predicted a live birth. Importantly, the day of embryo transfer (days 2–6), the number of embryos transferred during the fresh transfer, the method of insemination (IVF or intracytoplasmic sperm injection) and the stimulation protocol were not significantly related to live births (Table 1) and were not included in the model. The negative attribute of the number of thaws in the regression model was a reflection of extreme oocyte numbers where multiple thaws failed to achieve conception. When the oocyte number was limited, thaw number became a positive attribute but the other parameters were unchanged. There were significantly more FET attempts where at least one live birth occurred ($P < 0.001$).

Since the productivity rate model looks only for the presence or absence of live births, multiple regression analysis was used to estimate the number of live births per collection. This model predicts the number of live births by the following equation: 1.08 + 0.029(embryos) + 0.032(thaws) + 0.04(embryos frozen) + 0.1(fresh embryos transferred) − 0.02(age) − 0.01(oocytes) − 0.02(attempts).

Discussion

This study reviewed all standard assisted reproduction cases at PIVET Medical Centre between 2003 and 2011. The 9-year period provides power and scope to the study incorporating a range of stimulation techniques from long down-regulation to

flare, antagonist and agonist models, a movement from double- to single-embryo transfers, increasing exploration of blastocyst transfers, movement from slow freezing to vitrification methodology, plus numerous staff and other logistical changes. In contrast, the embryo culture system has been constant over this time. This study chose oocytes as the base fixed variable rather than embryos or transfers because it allowed the inclusion of cases of failed fertilization or transfer and freeze-all cycles in the model. The regression modelling has shown that these management developments have had little impact on the productivity rate that is centred on the contributions of repeated transfers make to a live birth outcome.

This study has shown that by applying the productivity rate model to the number of oocytes, there is a clear linear rise in the likelihood of a couple having a live birth as more oocytes are recovered (**Figure 1**). This effect was due to the additional contribution of frozen embryos to the productivity rate and was both oocyte number and age dependent. When five or fewer oocytes are recovered, the live birth rates per collection and per fresh transfer were similar, suggesting frozen embryos had little influence on final outcomes. However when more than five oocytes were recovered, live births per fresh transfer varied little with egg numbers while the contributions of FET to rates per collection saw the productivity rate rise in a linear and predictable manner to rates of 50–60% over the whole patient population. As may be expected, it was age dependent, with productivity rate for women $<$35 years reaching rates of 70–80% per collection when the oocyte numbers exceeded 13 oocytes (**Figure 2**). Even at modest egg numbers of 8–12 oocytes, where the risk of OHSS is low, productivity rate of 50–70% were observed. In other words, for younger women, the chance of a live birth was 20–40% for egg numbers $<$6 rising to 50–70% when egg numbers were 6–12. The productivity rate also rose for women aged 35–39 years but the relationship was more restrained, approaching 40% chance of a live birth per collection when egg numbers ranged 8–12. Unfortunately, for women aged $\geq$40 years, the productivity rates were not related to egg numbers approaching 20% with 11–14 oocytes but reducing with more oocytes. High egg numbers in older women were associated with very poor outcomes suggesting some detrimental interaction of hyper-response and age, an observation not previously reported.

The linear relationship between live births per collection and egg numbers is largely due to the increased number of FET cycles that are attempted subsequent to the collection cycle. Looking at the productivity rate per fresh and frozen transfers, both increased significantly with oocyte recovery rates but these rises were modest compared with viewing them per collection. The rates per transfer with egg numbers presumably reflect the quality of the 'best' embryo(s). There are two observations that can be made. One is that over all age groups, fresh transfers can only deliver rates of about 30% live birth per transfer and this rate will be dependent on the age matrix of each clinic's demographics. Secondly, the live birth rate per transfer appears very stable for 6–16 oocytes, refuting claims that an elevated hormonal environment is detrimental. While fresh rates above 16 eggs did not continue to rise as anticipated (Sunkara et al., 2011), there were fewer collections and transfers and these were cases deemed at minimal risk of OHSS. Where the risk of OHSS was considered likely, all the embryos were frozen and these collections are not represented in the fresh transfer data. The rates are therefore less reliable such that the impact of high hormone concentrations is less clear and negative effects at very high harvest rates, an observation suggested from the linear regression models, cannot be ruled out. Women who produce more than 20 oocytes usually exhibit polycystic ovary syndrome symptoms and it is possible the proportion of viable embryos may be less.

Logistic regression modelling identifies the number of embryos and the subset number of embryos that are frozen as key variables in predicting the chance of one or more live births per collection. Other variables such as the stimulation protocol, the method of insemination, the day of transfer or the number of embryos transferred were not found to be significant indicators in this oocyte number model. This is not surprising considering that these variables may influence the proportion of embryos frozen at low egg numbers but as the harvest rates rise, have less impact. Ultimately, the number frozen is the key determinate of the number of thaws that are possible from any cohort. This is further clarified by the significant contribution of live births from frozen embryos to the total number of live births as oocyte number increases (**Figure 3**). For oocyte numbers $<$8, only 20% of conceptions are from frozen embryos while for 8–16 oocytes, about 40% are from FET cycles. The impact of freeze-all cycles is observed above 16 eggs. Similarly, the mean number of FET cycles per collection was also directly linked to egg numbers with 0.8 cycles per collection when between 9–15 oocytes were harvested (**Figure 3** insert). Remember that once a live birth has been achieved, then a limited number of couples will return for another cycle, so this is an underestimate of the potential productivity rate. In many cases, the remaining embryos will be discarded or donated.

However not all frozen embryos are of similar quality to those embryos transferred as fresh embryos. When the number of live births per oocyte or embryo were analysed as a function of oocyte numbers, these key performance indicators fell from values of 10% with few oocytes to less than 5% with excessive oocyte numbers (**Figure 4**). In contrast and paradoxically, the number of live births per embryo transferred significantly rose with oocyte recovery rates, highlighting the practice that with more embryos available the embryos selected for transfer are of increasingly better quality. Rates of 20% live births per transferred embryo suggest that this may reflect the actual likelihood of a viable implantation per embryo when spread over all transfers over all ages (not just the best embryo in the best prognosis cases). The increased selection opportunities that having more oocytes provides is illustrated in **Figure 5**, where the significant decrease in the proportion of frozen embryos found suitable for transfer after thawing is documented. The interpretation of this is that either the overall oocyte quality diminishes with harvest rates or there are changes in management practice whereby more embryos are discarded. One practice could be that FET cycles may involve the thawing of more embryos than required followed by extended culture to day 5, the transfer of one blastocyst and the discarding (or refreezing) of the balance. In other words, more oocytes allows more embryos to be frozen,

which in turn permits greater selection in embryo quality on thawing, which in turn leads to an increase in the likelihood that the couple will achieve one or more live births from the egg collection with the fewest number of transfers.

The data suggest that while many follicles induced to develop by ovarian stimulation are able to deliver oocytes that have the potential to fertilize and cleave, far fewer have the potential to produce live offspring. There is ample evidence that not all mature follicles are functional (Van Blerkom et al., 1997) and the follicular environment is highly variable and related to pregnancy (Wallace et al., 2012). This study provides some insight into how few viable follicles actually exist in an ovarian stimulation cycle.

One criticism of using oocytes as a measure is that many are recovered from small follicles and that these would never be expected to deliver a pregnancy. Oocyte numbers are the gold standard measure for all reporting and publications even though they are heterogeneous in quality. This study has used a productivity rate approach to explore the relationship between oocyte numbers and the opportunity for repeated FET cycles to better understand the implications of pursuing a minimal stimulation model. Despite this, there is no clear optimal number of oocytes to aim for as a goal when deciding on the degree of stimulation except to avoid OHSS, nor is there any recognized policy on how to manage the frozen embryo asset to give the best prognosis to the couple. This is more relevant when considering the impact of minimal stimulation that seeks to address some of these risks of OHSS by reducing or removing the dependence on ovarian stimulation. It aims to reduce the number of collected oocytes, promoting a model of repeated, less-invasive treatment cycles (Zhang et al., 2010). However, repeated treatment cycles, while minimizing clinical risks, do incur other costs especially during egg collection and risks (such as patient distress) of not proceeding to embryo transfer. An alternative approach is to attempt to individualize treatment such as has been previously reported using the PIVET algorithm (Yovich et al., 2012), where an attempt was successfully made to reduce the risk of OHSS by using an empirically derived dosage regimen to minimize excessive recruitment based upon anti-Müllerian hormone, antral follicle count, FSH and previous history. The problem in attempting to individualise stimulation regimens is firstly the difficulty in identifying target groups (Nardo et al., 2011) and secondarily that there is no clear 'optimal' egg number to target if the couple's chance of pregnancy is not diminished by such action.

The linear and logistic regression models used here targeted only the likelihood of a couple delivering one or more babies as a result of a single egg collection. While the use of multiple regression analysis to attempt to define the productivity per oocyte, embryo or transferred embryo may be of value to scientific or pharmaceutical staff, the productivity of a cycle via all its transfer events is measured from a clinical or patient's perspective. This model ignores whether one, two or more than two babies result from an embryo transfer. From a clinical or patient's perspective, it was a successful outcome. The number of births resulting from multiple transfers using embryos created from a single collection is very small but it is a limitation of this model. With the increasing trend to single-embryo transfer procedures, this minor limitation will become irrelevant and could result in an increased productivity rate due to more FET procedures arising from a single TVOA.

When a couple undertakes an assisted reproduction cycle, their aim is to have a family. For some, this may be only one child, while for others, it may be many children. They are interested in achieving this as quickly and as cheaply as possible. In the early days of IVF, this may have been achieved with the transfer of many embryos, to the cost of the children's and the mother's welfare. Current protocols minimizing the risk of multiple pregnancy means that more than one transfer may be needed to meet the couple's family expectations. Whether these arise from repeated egg collections or from a combination of fresh and frozen transfers is of less concern to couples as long as the cost and time is minimized. However, it is important to clinicians and clinics, which need to consider the couple's family expectations when constructing a stimulation regimen for them. Current arguments to minimize stimulation regimens by limited gonadotrophin exposure focus on the egg collection as the primary vehicle for egg recovery while disregarding the contributions that FET cycles can make and going against the ovarian stimulation model routinely employed. All the activity of the clinic, the clinical management with drugs and other interventions including blood tests and ultrasound scans, all the physical, financial costs and medical risks to the patient and the likelihood of a pregnancy ultimately revolves around clinical decisions on a defined dose of gonadotrophin, when to induce ovulation, the recovery of oocytes, the fertilization method, usually intracytoplasmic sperm injection, progressive embryology management and finally transfer or cryopreservation of embryos. While the egg collection is the primary activity for all assisted reproduction treatment, it also carries all the risk and costs to the woman and the child (Halliday et al., 2010; Healy et al., 2010). In contrast, little attention has been placed on the minimal intervention, cost and risk that occur during an FET cycle.

This study has used the term 'productivity rate' for several reasons. The first was to avoid confusion with the similar term 'cumulative pregnancy rate'. The latter term has been used in various other ways, for instance to define consecutive cycles for life-table analysis (Haentjens et al., 2009; Osmanagaoglu et al., 2003; Shulman et al., 2002; van Disseldorp et al., 2007; Verpoest et al., 2009). Clarifying the terminology, Zegers-hochschild et al. (2009) representing the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) in their *Revised Glossary on ART Terminology* defined CPR as '... the estimated number of deliveries with at least one live born baby resulting from one initiated or aspirated ART cycle including the cycle when fresh embryos are transferred, and subsequent frozen/thawed ART cycles'. There have been several recent publications where CPR methodology was used as recommended, such as analysing the impact of single-embryo and double-embryo transfers including both fresh and frozen transfers from a single collection (De Neubourg et al., 2010; Lundin and Bergh, 2007), fresh and frozen oocytes (Borini et al., 2006; Romano et al., 2010; Ubaldi et al., 2010), natural and stimulated cycles (Pelinck et al., 2008) and highly purified human menopausal gonadotrophin to recombinant FSH (Wex-wechowski et al., 2010).

Notwithstanding that some may regard CPR and productivity rate as synonymous expressions, this study uses 'productivity rate' to specifically highlight its concept as a key performance indicator which may be universally applicable when comparing different treatment models. At its heart is the view that it seeks to be independent of minor variables such as the day of transfer or the number of embryos transferred and to focus on the delivery of patient-orientated outcomes — a live birth from an egg collection event. This study group believes that this view is vindicated given that these variables were specifically excluded from the regression models that look at the final endpoint rather than outcomes of individual transfers. In many other reports, failed fertilizations and freeze-all cycles are excluded whereas in this model they are easily managed. The productivity rate is at best a minimal rate since not all women will have all their frozen embryos transferred because they may not have returned for subsequent pregnancies or they may have achieved the number of children that meets their needs for family. The remaining embryos will ultimately be discarded or donated and since this may extend to 10 years or more, the number of live births will never reflect all the competency of all oocytes collected. This is not necessarily a criticism of using this, rather an acknowledgement that it is an underestimate of the true value. Productivity rate by definition needs to be conducted over a reasonably long time and is another limitation of its use. Ironically, the model may also be used in a general attempt to minimize the unnecessary freezing of embryos by relating the couple's expectation against the number of oocytes the clinician plans to recover.

The impact of oocyte numbers on the health and welfare of the children has not been considered in this study. These data do not support the suggestion that elevated hormone concentrations are detrimental to pregnancy resulting from either fresh or frozen embryo transfer. Suggestions that all embryos should be frozen and transferred back via FET are not supported by these observations. However, if future studies find associations between increased paediatric risk or diminished childhood welfare and the hormone environment associated with fresh embryo transfers, then these data may also be used to provide confidence that the consequences of freeze-all and repeated FET cycles on the CPR will all be unaffected.

In summary, this article seeks to define a couple's chance of pregnancy not by the age of the woman, but by her response to stimulation. While age or anti-Müllerian hormone may be helpful to a clinician and a couple prior to starting their first treatment, oocyte numbers are the key determinate of success, primarily because of the contributing effect of embryo freezing and thawing. Each regimen that seeks to significantly reduce the number of oocytes recovered, regardless of age will diminish the overall chance of a couple achieving a live birth and increase the necessity of a repeat stimulation cycle. Age may influence the number of oocytes, but it is the number of oocytes that directly controls outcome. While stimulation type, day of transfer or the number of embryos transferred are of interest, they do not play a significant effect on a live birth. Only the number of thaw cycles contributes to an increase in live births and thereby a higher productivity rate. These data may be used to enable clinics to set individualized targets for egg collections that are a balance between the risks of hyperstimulation, costs and time constraints of the patients and the knowledge that each additional FET has the potential to increase the likelihood of pregnancy when viewed through a productivity rate model. It implies a need to aim for a reasonable number of oocytes (e.g. 8—12) from any stimulated cycle in order to confer the full benefits denoted by the productivity rate.

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