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ASSISTED REPRODUCTION TECHNOLOGIES

# Embryo wastage rates remain high in assisted reproductive technology (ART): a look at the trends from 2004–2013 in the USA

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**Abstract** This work examined the trend in "embryo wastage" rates after ART in USA and its relationship to the number of embryos transferred, live born infants delivered across patient age, and the yearly percentage of embryos wasted. The data were obtained from the US-clinics SART databank for the years 2004–2013. A total of 1,808,082 non-donor embryos were transferred in 748,394 fresh cycles resulting in 358,214 liveborn. During the years of analysis, the mean number of embryos transferred has progressively decreased leading to an overall significant decrease in Embryo Wastage rates (83.2 to 76.5%, $p < 0.001$) while the percentage of transfers leading to a live born increased (24.8 to 27.8%, $p = 0.002$). Embryo Wastage negatively correlated with percentage of transfers resulting in live birth ($p = 0.001$), and the average number of embryos transferred positively correlated with the percentage of embryos wasted ($p < 0.001$). The overwhelming majority of embryos transferred still do not result into a live birth confirming that only few embryos per ART cycle are competent. The overall "Embryo Wastage" rates have consistently decreased from a high of 90% in 1995 to a rate of 76.5% in 2013. Transferring fewer embryos particularly at the blastocyst-stage and improved methods of embryo selection may further decrease "Embryo Wastage" rates.

*Capsule* The overall "Embryo Wastage" rates have consistently decreased from a high of 90% in 1995 to a rate of 76.5% in 2013. Transferring fewer embryos particularly at the blastocyst-stage and improved methods of embryo selection may further decrease "Embryo Wastage" rates.

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**Keywords** Assisted reproductive technology · In vitro fertilization · Embryo transfer · Embryo Wastage · Blastocysts · Delivery rate

## Introduction

The use of assisted reproductive technology (ART) procedures to treat infertile couples has significantly increased in the USA since its inception in the late 1970s. According to the Society for Assisted Reproductive Technology (SART), a total of 87,089 fresh, non-donor, in vitro fertilization (IVF) cycles were performed in 2013 and it is projected that IVF utilization rates will continue to climb [1].

Despite significant advancements in the field, the process of human reproduction remains inefficient with many unanswered biological questions [2, 3]. Previous work analyzed the number of embryos transferred compared to the number of live births and showed that the majority of embryos produced during IVF cycles (about 85%) and chosen for transfer fail to result in a live born infant [4]. One of the critical challenges in the field remains our ability to identify competent embryos that are capable of becoming a liveborn infant. Several strategies have been implemented thus far to assist embryologists and clinicians in choosing the best embryos for transfer and for improving pregnancy rates per transfer. Morphologic criteria to grade embryos correlate poorly with pregnancy and live birth rates and fail to identify chromosomally normal embryos [5–7]. The utilization of time-lapse embryo growth monitoring systems has also gained popularity, but data convincingly demonstrating improved outcomes as a result of this technology is still lacking [8–14].

Recent improvements in pre-implantation genetic screening (PGS) techniques for identifying normal euploid embryos have been associated with higher pregnancy and delivery rates when analyzed per transfer [15–17]; however, several barriers

to its widespread use still exist, including cost and particularly the lack of unequivocal evidence that its use improves pregnancy and live birth rates, particularly for patients with few embryos available for testing, due to the presence of high rates of mosaicism in the trophoblast cells [18–23]. Other studies have reported on the use of proteomics and metabolomics to identify factors in embryo culture media that may be predictive of embryo competence or assessing gene expression in cumulus cells; however, even these methods are still inefficient and not ready yet for clinical application [24–27].

Therefore, despite better embryo culture conditions encouraging embryo transfers at the blastocyst-stage, there is still lack of an ideal method for identifying competent embryos and thus the practice continues in transferring more than a single embryo, hoping that at least one will ultimately implant. The American Society of Reproductive Medicine (ASRM) recommends the transfer of a single embryo (blastocyst) in women younger than 35 years of age with a favorable prognosis [28, 29]. However, despite the fact that the use of elective single embryo transfer in this good prognosis patient group has increased over the years, it still remains relatively low. In the USA (as of 2013), single embryo transfer was in fact performed in only 10.5% of all fresh ART cycles, which is increased from a rate of 0.4% in 2004 [30]. Women continue to be aggressively stimulated with high doses of gonadotropins with the goal of retrieving multiple oocytes to increase the number of embryos available for transfer. This approach, however, is associated with a number of risks including ovarian hyperstimulation syndrome and increased cost due to the high doses of medications used. Furthermore, the practice of transferring more embryos carries the risk of multiple gestations, which is associated with increased maternal and perinatal morbidity and mortality [30–33].

A common paradox is that despite the practice of producing multiple embryos the overwhelming majority of embryos transferred do not implant or do not result in a live birth and are thus "wasted." The goal of this paper is to examine whether "Embryo Wastage" rates have changed in the past decade since we last reported on embryo attrition rates and to clarify its relationship to the number of embryos transferred, live born infants delivered, and patient age [4]. The aim of this study was to continue examining the trend in number of embryos transferred and the overall and age-specific wastage rates and live born infants between 2004 and 2013.

## Materials and methods

This is a retrospective study utilizing information published in the Society for Assisted Reproductive Technology (SART) and the Centers for Disease Control (CDC) and Prevention databases regarding utilization and success rates of ART procedures each year in the USA [1]. These databases were reviewed from 2004 through 2013 and the following data were collected for each year: total number of fresh non-donor IVF cycles, number of transfers performed, mean number of embryos transferred per procedure, number of liveborn infants, and percentage of transfers resulting in a live birth. Only cycles utilizing fresh non-donor eggs and fresh embryos were included in the data analysis. To determine the total number of embryos transferred, the mean number of embryos transferred per procedure was multiplied by the number of transfers performed. For the summary data that included information for all age groups between 2004 and 2013, the total number of embryos transferred was calculated by adding the number of embryos transferred each year in all the age groups. To best estimate the mean number of embryos transferred for all patients in all age groups, the total number of embryos transferred was divided by the total number of transfers performed. Embryo Wastage rate or the percentage of embryos that

**Table 1** Summary statistics of Embryo Wastage rates across *all ages* in non-donor ART cycles in the USA (2004–2013)

| Year | Mean number of embryos transferred | Number of transfers performed | Total number of embryos transferred | Number of liveborn infants | Embryo wastage rate (%) | Transfers leading to liveborn infant (%) |
|---|---|---|---|---|---|---|
| 2004 | 2.75 | 70,442 | 194,415 | 32,547 | 83.2 | 24.8 |
| 2005 | 2.67 | 71,379 | 190,944 | 33,083 | 82.6 | 25.0 |
| 2006 | 2.58 | 72,908 | 188,266 | 34,610 | 81.6 | 26.2 |
| 2007 | 2.50 | 75,677 | 189,923 | 36,555 | 80.7 | 26.8 |
| 2008 | 2.48 | 79,302 | 197,033 | 39,091 | 80.1 | 27.3 |
| 2009 | 2.40 | 78,797 | 189,634 | 38,663 | 79.6 | 27.4 |
| 2010 | 2.31 | 78,282 | 180,838 | 38,493 | 78.7 | 27.5 |
| 2011 | 2.22 | 78,266 | 174,528 | 37,003 | 78.7 | 27.1 |
| 2012 | 2.16 | 75,260 | 163,128 | 35,440 | 78.2 | 27.2 |
| 2013 | 2.04 | 68,081 | 139,373 | 32,729 | 76.5 | 27.8 |
| *Total* | | *748,394* | *1,808,082* | *358,214* | *80.1* | |

did not lead to a liveborn infant for each year was then calculated using the following formula: 100—(number of liveborn infants/number of embryos transferred × 100) as previously reported [4]. Trends from 2004 through 2013 across different SART age groups (under age 35, age 35–37, age 38–40, age 41–42, age greater than 42) were also evaluated.

Data analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistics, Version 22, 2013). Spearman rank-correlation coefficients and Pearson correlations were calculated. *P* values less than 0.05 were considered statistically significant.

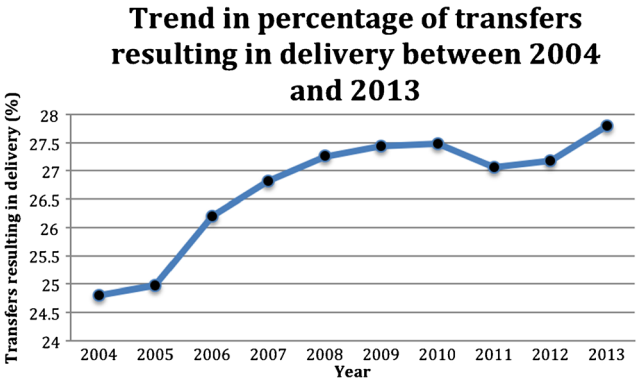


**Fig. 2** Trend in percentage of transfers resulting in delivery between 2004 and 2013

## Results

In the USA, between 2004 and 2013, the total number of transfers in fresh non-donor cycles was 748,394, the total number of embryos replaced was 1,808,082, and the total number of live born infants was 358,214, for an overall (across all ages and across the 10 years) "Embryo Wastage" rate of 80.2% (Table 1). The total number of fresh non-donor IVF cycles was 86,985 in 2004, peaked at 97,187 in 2008, and then slowly decreased to 87,089 in 2013. Similarly, the total number of transfers performed was 70,442 in 2004, peaked at 79,302 in 2008, and then decreased to 68,081 in 2013. Interestingly, the overall mean number of embryos transferred has steadily decreased from an average of 2.75 in 2004 to 2.04 in 2013 and, this trend, seen across all age groups, was significant (Fig. 1, $p < 0.001$). Examining the trend in mean number of embryos transferred over the last 20 years, the reduction in the mean number of embryos transferred is even more striking since in 1995 it was 3.9 [4]. The number of transfers resulting in a live birth has increased each year across all age groups (Fig. 2, $p = 0.002$). The increase was statistically significant in all age groups with the exception of the group of women age greater than 42. In 2004, the overall Embryo Wastage rate, meaning the number of embryos that did not lead to a live birth, was 83%, which decreased to 76.5% in 2013 and this trend was statistically significant (Fig. 3, $p < 0.001$). This represents a continued improvement since in 1995 about 91% of the embryos transferred did not produce a live birth [4].

When age groups, as reported in SART, were analyzed individually (Tables 2, 3, 4, and 5), "Embryo Wastage" rates decreased ($p < 0.05$) across all age groups and it was more pronounced in the younger women, particularly for the group of women under the age of 35. In fact, for the under 35 group, "embryos wastage" decreased from 76.1% in 2004 to 65.2% in 2013 ($p < 0.001$).

In the group of women over the age of 42 (Table 6), the "Embryo Wastage" rate only marginally decreased and remained relatively high from 2004 to 2013 (98.0 to 97.2%, respectively, $p < 0.05$); in this age group, there was also the smallest, albeit still significant ($p < 0.001$), change in the mean number of embryos transferred (3.3 in 2004 to 2.8 in 2013). However, the correlation between average number of embryos transferred and "Embryo Wastage" disappears in women over the age of 42.

Data analysis further showed that the average number of embryos transferred per year, averaged across all age groups, positively correlated with the "Embryo Wastage" rate (Spearman coefficient = 0.988, $p < 0.001$). This illustrates that as the number of embryos transferred decreased the percentage of non-implanting embryos also decreased without having an

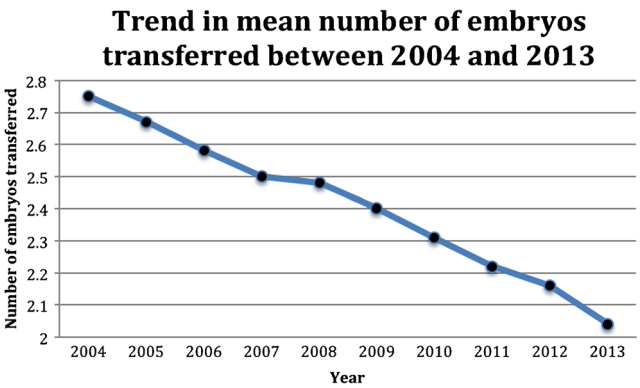


**Fig. 1** Trend in mean number of embryos transferred between 2004 and 2013

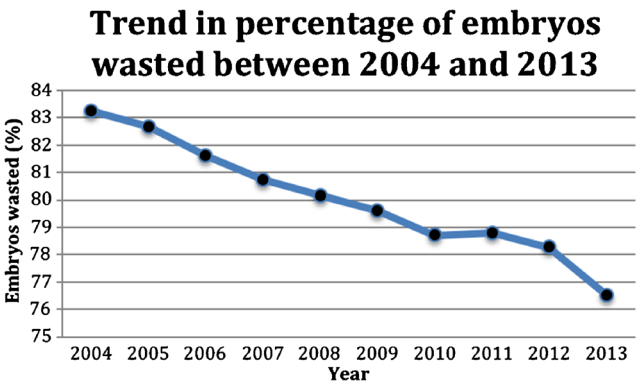


**Fig. 3** Trend in percentage of embryos wasted between 2004 and 2013

**Table 2** Embryo Wastage rate for all non-donor ART cycles in women *younger than 35 years* in the USA (2004–2013)

| Year | Mean number of embryos transferred | Number of transfers performed | Total number of embryos transferred | Number of liveborn infants | Embryo Wastage rate (%) | Transfers leading to liveborn infant (%) |
|---|---|---|---|---|---|---|
| 2004 | 2.5 | 32,117 | 80,292 | 19,162 | 76.1 | 42.5 |
| 2005 | 2.4 | 31,906 | 76,574 | 19,293 | 74.8 | 43.3 |
| 2006 | 2.3 | 32,122 | 73,881 | 19,861 | 73.1 | 44.9 |
| 2007 | 2.2 | 33,153 | 72,937 | 21,097 | 71.1 | 46.1 |
| 2008 | 2.2 | 34,595 | 76,109 | 22,596 | 70.3 | 47.3 |
| 2009 | 2.1 | 34,407 | 72,255 | 22,512 | 68.8 | 47.5 |
| 2010 | 2.0 | 34,383 | 68,766 | 22,497 | 67.3 | 47.8 |
| 2011 | 1.9 | 34,430 | 65,417 | 21,490 | 67.1 | 46.3 |
| 2012 | 1.9 | 33,382 | 63,426 | 20,926 | 67.0 | 47.1 |
| 2013 | 1.8 | 31,039 | 55,870 | 19,419 | 65.2 | 47.7 |
| *Total* | | *331,534* | *705,527* | *208,853* | *70.4* | |

impact on the pregnancy rates. This pattern has been consistent since 1995 and is further proof that only a few embryos, if any, are competent for live birth per cohort in each ART cycle [4]. In other words, the decrease in wastage rate observed is not due to an improved oocyte or embryo biology, but merely to a reduction in the mean number of embryos transferred (i.e., a smaller denominator in the equation of total live births divided by total number of embryos transferred). The percentage of transfers leading to a liveborn infant was negatively correlated with the "Embryo Wastage" rate (Spearman coefficient = −0.867, $p = 0.001$) meaning that as the delivery rate increased, the 'Embryo Wastage" rate decreased.

## Discussion

The summary statistics for ART procedures in the USA over the last decade confirm that the vast majority of embryos (80%) produced during IVF and chosen for transfer still fail to implant or to result in a liveborn infant. However, the "Embryo Wastage" rates have significantly decreased over the past decade (83 to 76.5%, respectively, $p < 0.001$) and the explanation for this decline is a significant reduction during this time of the mean number of embryos transferred (from 2.5 in 2004 to 1.8 in 2013, $p < 0.001$). The fact that the vast majority of embryos do not become a live birth and that the overall, all ages combined, live birth rate per embryo transfer have remained stable at about 27% for the last 10 years is a further proof that despite progress in the development of stimulation protocols and progress in embryology laboratories, human reproduction remains inefficient whether in vivo or in vitro.

The question remains: can ART outcomes, i.e., pregnancy rates per transfer, live birth rates per transfer, and implantation rates, actually be improved? Perhaps, but several factors need to be considered. First, if not all the embryos are competent to

**Table 3** Embryo Wastage rate for all non-donor ART cycles in women *age 35–37* in the USA (2004–2013)

| Year | Mean number of embryos transferred | Number of transfers performed | Total number of embryos transferred | Number of liveborn infants | Embryo Wastage rate (%) | Transfers leading to liveborn infant (%) |
|---|---|---|---|---|---|---|
| 2004 | 2.7 | 15,994 | 43,184 | 7723 | 82.1 | 35.5 |
| 2005 | 2.6 | 16,796 | 43,670 | 8086 | 81.5 | 35.8 |
| 2006 | 2.5 | 17,483 | 43,707 | 8695 | 80.1 | 37.4 |
| 2007 | 2.5 | 17,963 | 44,908 | 8879 | 80.2 | 36.9 |
| 2008 | 2.4 | 18,101 | 43,442 | 9049 | 79.2 | 37.3 |
| 2009 | 2.3 | 17,057 | 39,231 | 8609 | 78.1 | 38.2 |
| 2010 | 2.2 | 16,843 | 37,055 | 8506 | 77.0 | 38.4 |
| 2011 | 2.1 | 16,542 | 34,738 | 8317 | 76.1 | 38.4 |
| 2012 | 2.0 | 16,198 | 32,396 | 7819 | 75.9 | 37.9 |
| 2013 | 1.9 | 14,821 | 28,160 | 7465 | 73.5 | 39.2 |
| *Total* | | *167,798* | *390,491* | *83,148* | *78.7* | |

**Table 4** Embryo Wastage rate for all non-donor ART cycles in women *age 38–40* in the USA (2004–2013)

| Year | Mean number of embryos transferred | Number of Transfers performed | Total number of Embryos transferred | Number of Liveborn infants | Embryo Wastage rate (%) | Transfers leading to Liveborn infant (%) |
|---|---|---|---|---|---|---|
| 2004 | 3.1 | 13,766 | 42,675 | 4472 | 89.5 | 25.3 |
| 2005 | 3.0 | 13,780 | 41,340 | 4489 | 89.1 | 25.4 |
| 2006 | 2.9 | 14,020 | 40,658 | 4709 | 88.4 | 26.7 |
| 2007 | 2.8 | 14,709 | 41,185 | 5072 | 87.7 | 27.2 |
| 2008 | 2.7 | 16,063 | 43,370 | 5819 | 86.6 | 28.2 |
| 2009 | 2.7 | 16,459 | 44,439 | 5,867 | 86.8 | 28.3 |
| 2010 | 2.6 | 16,283 | 42,336 | 5,765 | 86.4 | 28.1 |
| 2011 | 2.5 | 15,805 | 39,512 | 5,435 | 86.3 | 27.5 |
| 2012 | 2.4 | 14,332 | 34,397 | 5,030 | 85.4 | 28.5 |
| 2013 | 2.3 | 12,516 | 28,787 | 4,393 | 84.7 | 28.5 |
| *Total* | | *147,733* | *398,699* | *51,051* | *87.2* | |

produce a live birth, we must find an accurate and consistent method for identifying the most competent ones for transfer. Strides are being made in the field with the recent increase in the number of ART cycles utilizing preimplantation genetic screening on trophectoderm biopsy and analysis by next generation sequencing to identify chromosomally normal embryos for transfer. In the group of women older than 40 years studies with PGS on trophoblast cells have shown that a large number of embryos produced are chromosomally abnormal, thus explaining at least in part why there is such high "Embryo Wastage" in this age group [16, 34]. However, it remains to be seen whether this technique will ultimately lead to a significant improvement in live birth rate since it is still error-prone with the risk of discarding embryos wrongly diagnosed as aneuploidy because of mosaicism [21–23]. Other barriers such as the cost, including the possible need to cryopreserve embryos and defer transfer, and invasiveness of the biopsy and any potential long term effects also need to be addressed.

Second, exclusive blastocyst transfers may be one less costly and less invasive strategy than PGS for reducing the number of embryos transferred and thereby reducing Embryo Wastage rates without significantly compromising pregnancy rates. The recent literature on blastocyst transfers supports an improved pregnancy rate as opposed to cycle day 3 transfers [35, 36]. A move of all transfers to blastocyst-stage embryos will also improve the live birth rates per transfer by removing from the denominator the cases failing to reach blastocyst stage embryos. However, theoretical risks from prolonged culture of embryos on epigenetic errors still need to be kept under scrutiny.

Third, we should continue to develop non-invasive methods of embryo screening such as proteomics, metabolomics, and examination of oocyte and cumulus-cell gene expression [24–27]. Time-lapse technology has recently been adopted by several IVF clinics across the USA with some studies showing promising results regarding the technology's

**Table 5** Embryo Wastage rate for all non-donor ART cycles in women age 41–42 in the United States (2004–2013)

| Year | Mean number of Embryos transferred | Number of Transfers performed | Total number of Embryos transferred | Number of Liveborn infants | Embryo Wastage rate00 (%) | Transfers Leading to liveborn infant (%) |
|---|---|---|---|---|---|---|
| 2004 | 3.3 | 5,741 | 18,945 | 1,001 | 94.7 | 14.7 |
| 2005 | 3.3 | 5,919 | 19,533 | 1,026 | 94.7 | 14.9 |
| 2006 | 3.2 | 6,139 | 19,645 | 1,113 | 94.3 | 15.3 |
| 2007 | 3.1 | 6,328 | 19,617 | 1,214 | 93.8 | 16.4 |
| 2008 | 3.2 | 6,805 | 21,776 | 1,337 | 93.9 | 16.7 |
| 2009 | 3.1 | 6,931 | 21,486 | 1,403 | 93.5 | 17.0 |
| 2010 | 3.0 | 7,147 | 21,441 | 1,467 | 93.2 | 16.8 |
| 2011 | 3.0 | 7,552 | 22,656 | 1,472 | 93.5 | 16.6 |
| 2012 | 2.9 | 7,359 | 21,341 | 1,394 | 93.5 | 16.3 |
| 2013 | 2.7 | 6,179 | 16,683 | 1,171 | 93.0 | 16.3 |
| *Total* | | *66,100* | *203,123* | *12,598* | *93.8* | |

**Table 6** Embryo Wastage rate for all non-donor ART cycles in women age greater than 42 in the United States (2004–2013)

| Year | Mean number of embryos transferred | Number of Transfers performed | Total number of Embryos transferred | Number of Liveborn infants | Embryo Wastage rate (%) | Transfers leading to Liveborn infant (%) |
|---|---|---|---|---|---|---|
| 2004 | 3.3 | 2,824 | 9,319 | 189 | 98.0 | 6.0 |
| 2005 | 3.3 | 2,978 | 9,827 | 189 | 98.1 | 5.5 |
| 2006 | 3.3 | 3,144 | 10,375 | 232 | 97.8 | 6.7 |
| 2007 | 3.2 | 3,524 | 11,277 | 293 | 97.4 | 7.5 |
| 2008 | 3.3 | 3,738 | 12,335 | 290 | 97.6 | 6.8 |
| 2009 | 3.1 | 3,943 | 12,223 | 272 | 97.8 | 6.2 |
| 2010 | 3.1 | 3,626 | 11,241 | 258 | 97.7 | 6.3 |
| 2011 | 3.1 | 3,937 | 12,205 | 289 | 97.6 | 6.5 |
| 2012 | 2.9 | 3,989 | 11,568 | 271 | 97.7 | 6.1 |
| 2013 | 2.8 | 3,526 | 9,873 | 281 | 97.2 | 7.3 |
| *Total* | | *35,229* | *110,243* | *2,564* | *97.6* | |

ability to screen for healthy embryos that are most likely to implant. However, prospective studies are still needed to clarify algorithms for analyzing this data and proving, unequivocally, a significant benefit to patients [9]. Very recent randomized controlled trials have failed to show any benefit by adopting time lapse technology over morphology in improving pregnancy and delivery rates [13, 14].

Fourth, we can consider modifying our protocols of ovarian stimulation to avoid the production of too many oocytes, which, as demonstrated here and in previous studies, may not lead to more live births, but to increased "Embryo Wastages." Minimal stimulation or natural IVF cycles have been associated with improved egg quality and reduced aneuploidy rates [37–39]. Additionally, a reduction in the amount of medication used for stimulation would reduce the risk of ovarian hyperstimulation syndrome for high responders, and possibly be a more cost-effective strategy for poor responders [40, 41] and reduce the rates of oocyte aneuploidy [42]. Fifth, more studies are needed to address endometrial receptivity in fresh transfer versus deferred frozen embryo transfer cycles [43].

There are some limitations to this study. The data have been obtained from the SART-USA registry, reflecting embryo transfers policies and guidelines different from other countries. Even though our calculation of the overall "Embryo Wastage" rate is the best estimation of the true rate, we could have underestimated the wastage that actually occurs. We did not take into account the wastage of fresh embryos that are not amenable for or chosen for fresh transfer and are subsequently discarded. We also did not include embryos that were cryopreserved and could be transferred at a later time; however, for the years of analysis, the overwhelming majority of ART cycles allocated the best embryos for the fresh transfer.

In summary, despite today's greatly improved laboratory conditions and the individualization of stimulation protocols, the process of IVF remains inefficient with low live birth rates per embryos produced and transferred. The analysis of the years 2004–2013 showed that (a) there has been a decrease in the mean number of the embryos transferred; (b) an increase in pregnancy rates per transfer; (c) an increase in implantation rates; (d) and a notable reduction in the "Embryo Wastage" rate, mostly due to a reduced denominator, i.e., fewer embryos transferred. These results reinforce previous observations that the majority of the oocytes harvested and the majority of embryos produced during IVF are chromosomally or genetically abnormal [44, 45]. The time has come to strengthen and support research in methods to assess embryo competence for live birth before the transfer. The recent developments of PGS by next generation sequencing (NGS) on trophectoderm biopsies and mitochondrial DNA content analysis are still in need of large-scale validation with properly designed randomized controlled trials. In fact, recent reports have failed to show improvements in delivery rates due to the high rates of false positive diagnosis caused by trophectoderm mosaicism and sampling limitations. Until robust and validated methods of embryo selection are produced, the simplest strategy that could be employed immediately is performing embryo transfers only at the blastocyst stage of development and accepting the possibility that some IVF cycles may not result in a transfer.

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