World Journal of Biology Pharmacy and Health Sciences

eISSN: 2582-5542

Cross Ref DOI: 10.30574/wjbphs

Journal homepage: https://wjbphs.com/

(Research Article)

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Total numbers of embryos lost during in-vitro fertilization

Mary Dianke Zhao [1], Juliana Kathleen Upchurch [2] and Robert Allen Malkin [3,*]

[1] *International Research Institute of North Carolina, 500 Westover Drive, Sanford, NC 27330, United States.*
[2] *New York University School of Global Public Health, 708 Broadway New York, NY 10003, United States.*
[3] *Biomedical Engineering, Duke University, 101 Science Drive, Durham, NC 27708, United States.*

World Journal of Biology Pharmacy and Health Sciences, 2024, 19(03), 603–611

Publication history: Received on 08 August 2024; revised on 24 September 2024; accepted on 27 September 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.19.3.0666

Abstract

The objective of this study is to investigate the number of lost, viable embryos during Assisted Reproductive Treatments (ART), particularly in-vitro fertilization (IVF). The polarizing debate defining the beginning of human life presents the possibility of criminality associated with ART. Data from the CDC's ART database spanning 1996-2020 was categorized into donor and non-donor, frozen and fresh, by state and by maternal age. In total, there were 2.6 million lost viable embryos across the years studied, making this a leading cause of death in the US, if life is legally determined to begin at conception. We defined viable as any embryo that a trained technician cleared for transfer to a woman's uterus. There was considerable variation in embryo loss rates across states. Fourteen states had statistically significantly higher loss rates than average, while 27 states had significantly lower ($p<0.05$). A stricter legal definition of personhood did not correlate with higher rates of lost embryos in that state. There were also notable discrepancies in loss rates across individual clinics for the same given year, with some clinics having a 0% loss rate and others nearing 100%. Clinic-by-clinic variation indicates that there are significant differences in technique and experience and that traveling across state lines to receive reproductive healthcare may be driven by both legal and clinical outcomes.

Keywords: Assisted Reproductive Treatments (ART); *In Vitro* Fertilization (IVF); Embryos; personhood; State variation; Clinical variation

1. Introduction

There have always been discrepancies in defining personhood: When does life begin? Defining personhood is controversial and is closely tied to philosophy, religion, and law. If personhood begins at conception, every viable embryo is legally considered a person, and the death of that person could be a crime. Therefore, any person who puts a viable embryo at risk during a procedure could be committing a crime.

The first *in vitro* fertilization (IVF) procedure was performed nearly a half-century ago [1]. While the past five decades have been met with significant advances in technological resources, success rates, defined as live-birth, for women under 35 years of age have remained relatively constant at approximately 55% for the past twenty years [2]. Although success rates drastically decrease as women surpass age 35, for women under age 35, there is still wide variation in the frequency of live births. During the IVF procedure, only viable, fertilized eggs (embryos) are transferred to a woman's uterus. We used embryos that had been transferred because these are inspected and graded for viability, whereas fertilized but not transferred embryos have not received this inspection. Therefore, any embryo that is transferred but does not result in a live birth could be a crime, perhaps voluntary manslaughter, involuntary manslaughter, or murder, if life legally begins at conception. In fact, the Supreme Court of Alabama specifically ruled that embryos created for the purpose of IVF are children under the state's Wrongful Death of a Minor Act [3]. Seen from a different perspective, the

* Corresponding author: Robert A. Malkin

variability in the rate of live births indicates a large variation in the number of presumed viable embryos that do not result in a live birth.

While there is data, gathered by the US government, concerning IVF, and tracking lost embryos that were never transferred because they were not viable, but, since the embryos were not deemed viable, in this case the criminal risk is low. However, there has not been an analysis of the number of lost embryos that were considered viable and transferred. By contrast, in these cases, the criminal risk is high. The objective of this study is to analyze the numbers of lost, viable embryos and compare the proportion of lost embryos by state, age group, and individual clinics.

2. Material and Methods

The raw embryo transfer data was derived from the Assisted Reproductive Technology (ART) Database from the CDC for the years 1996-2020, excluding 2019 [4]. Data from 2019 was excluded because it was not differentiated by individual clinics.

Data was available from the CDC by age group, state, clinic, and whether the embryo was formed from a donor or non-donor egg. In some years, data was also further subdivided into donor fresh eggs or frozen embryos. For 2017, 2018, and 2020, CDC data for the fresh and frozen non-donor category was reported as a combined total.

We adopted the definitions as described by the CDC [5]:

- **Donor egg cycle.** An ART cycle in which an embryo is formed from the egg of one woman (the donor) and then transferred to another woman (the recipient). Sperm from either the recipient's partner or a donor may be used.
- **Donated embryo cycle.** An ART cycle in which an embryo that is donated by a patient or couple who previously underwent ART treatment and had extra embryos available is transferred to another woman (the recipient).
- **Fresh eggs, sperm, or embryos.** Eggs, sperm, or embryos that have not been frozen.
- **Fresh embryo cycle.** An ART cycle in which fresh (never frozen) embryos are transferred to the woman. The fresh embryos are conceived with fresh or frozen eggs and fresh or frozen sperm.
- **Frozen egg cycle.** An ART cycle in which frozen (cryopreserved) eggs are thawed and fertilized, and then the resulting fresh embryo is transferred to the woman. Frozen and thawed eggs may be fertilized with either fresh or frozen sperm.
- **Frozen embryo cycle.** An ART cycle in which frozen (cryopreserved) embryos are thawed and transferred to the woman. Frozen embryos may have been conceived using fresh or frozen eggs and fresh or frozen sperm.
- **Live-birth delivery.** The delivery of one or more infants with at least one born alive.

The total number of lost embryos is the total number of infants born subtracted from the total number of embryos implanted. It is assumed that all embryos implanted were viable, since a technician would not transfer an embryo that is known to be non-viable. To calculate the number of implanted embryos, we multiplied the average number of embryos implanted per transfer by the number of transfers. Where the average number of embryos transferred is not available for a particular year and clinic, we used the average of all the clinical averages from 2013 (<35 years of age (yoa): 1.87; 35-37 yoa: 2.04; 38-40 yoa: 2.31; 41-42 yoa: 2.62; 43-44 yoa: 2.78; >44 yoa: 2.63).

To find the total number of live births, we multiplied the percent of singleton live births by 100 and added it to the percent of twin live births times 100 times two. In instances in which the percent of twin live births is not provided, we subtracted the percent of singleton live births from the percent of all live births, assuming that if it was not a singleton live birth, it was assumed to be a twin live birth. This assumes that there were no triplets, quadruplets, and beyond. Where neither the percent of twin live births nor the percent of singleton live births is provided, we used the average percent of twin live births from 2013 to calculate the number of infants born. The average percentage of live births that were twins were as follows:

Table 1 The average percent of twin live births from 2013, by age group.

Age Group	<35	35-37	38-40	41-42	43-44	>44
Avg Percentage of Twin Live Births (2013)	30%	26%	20%	12%	5%	14%

Where there was a match in age groups for a year without the twin and triplet birth rates, the above rates were used. If the age groups did not match the list above in a year without the twin and/or triplet birth rates, then the average of the two nearest age groups was used.

Some clinics reported data in fractions and some in truncated percentages. Since there cannot be more than zero and less than one live birth per 100 transfers, clinics that reported truncated percentages were multiplied by 100 to get the number of live births per 100. However, because truncated percentages can lead to a non-integer number of embryos being calculated as lost, the number of lost embryos was rounded to an integer. Across years that had either “embryos from donor eggs,” “donor eggs,” or “embryos,” we combined those categories into one category (either “fresh donor” or “frozen donor”). If either the egg or embryo was frozen, that cycle was classified as frozen: if both the egg and embryo were fresh, the cycle was classified as fresh.

For 2011 and 2012, where the number of singleton and triplet (or more) births was provided but the number of twins was not, we calculated the number of twins per 100 by subtracting singletons and triplets from the total live births. In the few cases where the number of triplets was reported to be greater than 10% (impossibly high), the number of triplets was changed to zero.

2.1. Statistical Analysis

To determine if women’s increased age increases the percentage of lost embryos for frozen non-donor eggs, we used a one-tailed, two-sample test of proportions using a normal approximation. To investigate whether certain states lose more or less embryos than the overall average state proportion, we summed up all the lost embryos and embryos implanted for each state across all years, 1996-2020, to get the proportions for each state. A two-tailed, one-sample test of proportions (using a normal approximation) was used, with the average state proportion as the null. Furthermore, to see if certain clinics lose more or less embryos than the average clinic, clinics from 2020 were individually compared with the clinical average for that year using a two-tailed, one-sample test of proportions (using a normal approximation) with the average of all the clinic proportions as the null hypothesis.

3. Results

Between 300 and 500 clinics reported IVF data each year (Table 2). There was a total of 2.6 million viable, lost embryos between the years 1996-2020. Yearly losses ranged from 50,000 to over 200,000 (Table 3).

Table 2 Data Available: Number of Clinics Reporting by Year

Year	Number of Clinics Reporting
1995	361
1996	303
1997	336
1998	361
1999	371
2000	384
2001	385
2002	392
2003	400
2004	412
2005	423
2006	427
2007	431
2008	437

2009	442
2010	444
2011	452
2012	457
2013	469
2014	459
2015	465
2016	464
2017	449
2018	457
2020	450

Table 3 The Number of Lost Embryos per Year per Type

Year	FreshND	Frozen D	Fresh onor	Frozen Donor
1996		29261	13263	3776
1997		29585	15561	5160
1998		30121	16679	5615
1999		28479	14792	6334
2000		29967	16218	6562
2001		33634	17613	8119
2002		35358	17570	8912
2003		36014	17415	9792
2004		35166	17066	10164
2005		38545	16397	10988
2006		38932	16051	11409
2007		39734	15506	10895
2008		41601	15545	10626
2009		40459	13880	10389
2010		40597	12603	10544
2011	169940	42587	11308	10451
2012	138093	46282	10670	11091
2013	116213	53013	8655	11656
2014	99730	56835	6711	12155
2015	83336	62538	5090	12788
2016	70127	67528	5708	14381
2017	172111		9128	30893
2018	157256		5646	30809
2020	166391		4966	27636

Analyzing the data of embryos from frozen nondonor eggs, women under age 35 had a total of 409,020 lost embryos, and women older than 35 had a total of 447,216. Women in the <35 age group had a total proportion of 0.7555 of transferred embryos lost (about 76%), while women over 35 had a total proportion of 0.8043 lost (about 80% of transferred embryos were lost). There is a significant difference between the two age groups for every year studied between 1996 and 2020 ($p<0.05$, see Figure 1).

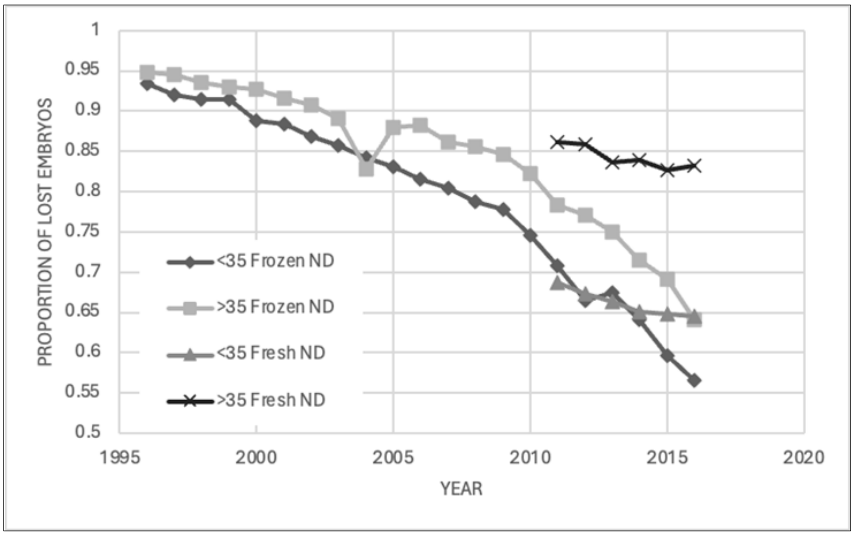

Figure 1 "<35" and ">35" refers to the age group of women (aged younger than 35 and older than 35, respectively). "ND" means the eggs in this category were nondonor. There is a significant difference between the two age groups for every year studied here between 1996 and 2016. Older women have a higher percentage of lost embryos almost every year, and this difference is even more prominent in the Fresh eggs ($p<0.05$, except 2004, frozen, non-donor)

There were significantly large differences between the US states. Twenty-seven states showed statistically significantly lower embryo losses than average, while fourteen showed statistically significantly higher losses ($p < 0.05$), the worst of which was Alaska with 93%, as compared to the best of which was Colorado with 64% of transferred embryos lost (see Figure 2).

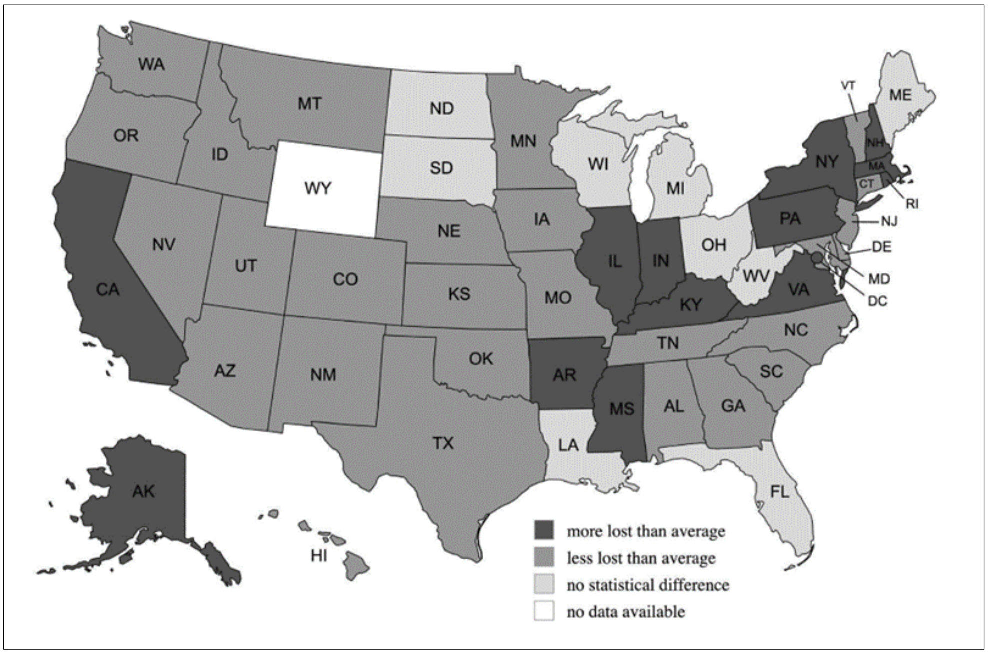

Figure 2 Twenty-seven states showed statistically significantly lower rates of lost embryos than the average state proportion, and 14 showed statistically significantly higher rates of lost embryos ($p < 0.05$)

Additionally, by analyzing the clinics from 2020, 81 of the 429 clinics had a significantly smaller proportion (average=0.290) of lost embryos than the average (0.642) of the clinics, 230 had a higher proportion (average=0.764), and 118 showed no statistical difference from the average. The range of lost embryos varied dramatically between clinics, ranging from nearly 0% in some to nearly 100% in others (see Figure 3).

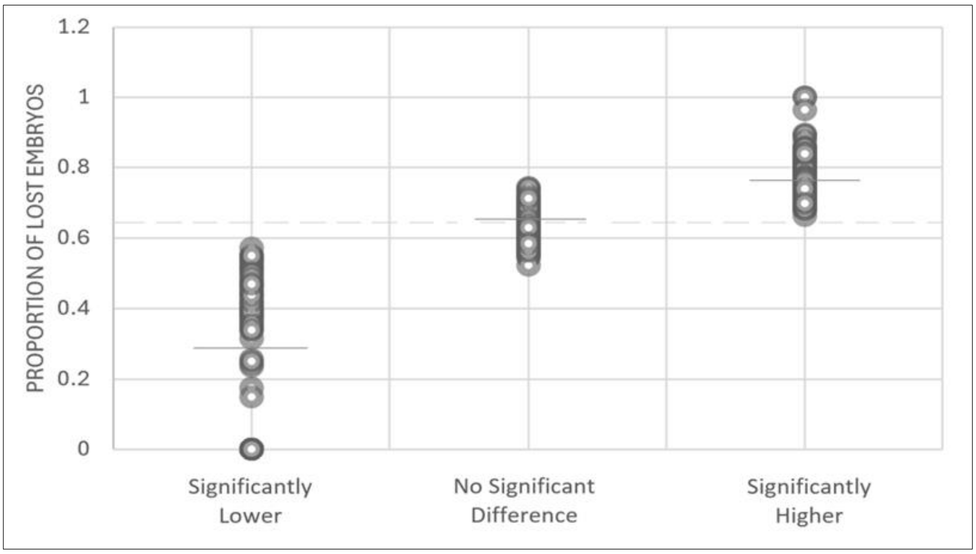

Figure 3 Eighty-one of the 429 clinics had a significantly smaller proportion of lost embryos than average, 230 had a higher proportion, and 118 showed no statistical difference from the average. The dotted line is the average of all clinics and the solid line is the average of each group. The range of lost embryos is very large, ranging from nearly 0 to nearly 100% of transferred embryos being lost.

4. Discussion

There are US states that consider or may soon consider personhood to start from conception. Twenty-three states have introduced legislature establishing fetal personhood [6]. In these states, a viable embryo is a legal life for whom the laws of the state apply and the loss of that embryo could be considered murder, voluntary, or involuntary manslaughter in those states. Our data shows that there have been millions of embryos lost during IVF over a 14-year period.

In fact, IVF is one of the top ten leading causes of death in the US under these assumptions. 42,514 people died in car crashes and 101,209 people died of diabetes in 2022 in the US [7, 8]. However, these are less than the average total lost embryos per year, which is 109,359. If embryos were considered citizens in every state, that would mean that embryos lost through IVF represent a significant portion of all deaths in the US and each one could be a crime.

There has always been debate about when or if an embryo could be defined to have "personhood." But more recently, the increase in personhood bills has stimulated debate over how state legislatures could impact IVF clinics, with people having concerns that the push for embryo rights could threaten IVF access [9, 10, 11]. Presumably, no clinician or technician at an IVF clinic would risk being prosecuted for a crime simply for transferring an embryo that they knew had a high chance of death.

As of now, 18 out of 50 states consider fetuses to be people at some point during pregnancy [12]. One would assume that these 18 states would have worse support for reproductive health, but that is not the case. Based on our results, it is not true that states with a stricter definition of personhood (that it starts earlier as a fetus) have a higher proportion of lost embryos (figure 2). Out of those eighteen states considering fetuses to be people at some point during pregnancy, only three states had a statistically significantly higher proportion of lost embryos than the overall average state proportion. Another three states had no statistical difference from the average, while the remaining twelve states, with this stricter definition of personhood, all had lower than average proportions of lost embryos. The state legislation on personhood for fetuses did not significantly impact the IVF outcomes or, apparently, resources, for IVF clinics in those states.

When seeking IVF treatment, patients are often looking for clinics that have high prestige and success rates. And there is some evidence that carefully selecting a clinic may influence the outcome of an IVF treatment. That suggests considerable difference in the quality of each clinic's techniques, the experience of their doctors, or the outside resources they can access [13, 14]. This issue of traveling for reproductive healthcare in the US is significant enough that it was specifically mentioned in the recent US Supreme Court decision, *Dobbs v. Jackson Women's Health Organization*. Justice Brett Kavanaugh wrote in that decision that one state may not "bar a resident of that State from traveling to another state to obtain an abortion … based on the constitutional right to interstate travel," [15]. As such, thousands of women travel for reproductive care such as IVF, contraception, and abortions [16, 17, 18, 19]. There has even been US legislation introduced to fund traveling for reproductive healthcare [20]. Based on our data from the year 2020, there is, indeed, a substantial difference between the clinics in the US, with the proportion of lost embryos being as low as 0 to as high as 100%, making travel for healthcare a medical as well as a legal decision.

Much research has been done on the association between increased maternal age and IVF outcomes. Women older than 35 are considered to be of advanced maternal age (AMA). Women over 35 experience a significant increase in embryo aneuploidy rate, partly due to the gradual decline in ovarian reserve and partly due to the decrease in oocyte/embryo competence, which is defined as the ability to produce a live birth [21]. The latter is due to many different processes such as shortening of telomeres and impaired mitochondrial metabolic activity [22, 23, 24]. The impact of AMA is similarly reflected in our results. Looking at the results from frozen nondonor eggs, for the ages under 35 the proportion of embryos lost was 0.7555, and 0.8043 for ages over 35.

There are limitations to our findings. We assumed that all transferred embryos were viable. However, in fact, there are grades of viability that are not captured in the CDC data. Economic factors, population size, number of cities, and the size of cities are all factors that could influence the state-to-state difference in IVF outcomes rather than solely the legislation on "personhood." In our analysis of data by state, Washington DC was counted as a state, and there was no data available for Wyoming. In our analysis of clinical preferences, we did not measure the "reputation," of each clinic, but only considered the performance reflected in the proportion of embryos lost. In our analysis of IVF outcome by age, there are factors such as female body mass index that were not accounted for in this study, though it has large influence on success rate [25].

5. Conclusion

This study shows that, if life begins at conception, IVF is one of the leading causes of death in the US. The numbers vary significantly by age, state, and individual clinic, meaning that travel between states to obtain reproductive healthcare would likely remain high, independent of personhood legislation. It is important to identify the magnitude and prevalence of this issue as nearly half of the US states are currently considering personhood legislation.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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