

Assisted Reproductive Technology

Meta Analysis

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ABSTRACT

Assisted reproductive technology (ART) includes fertility treatment where eggs or embryos are processed outside of the body to promote increased fertility rates and as a result successful births of healthy babies. ART procedures commonly use three types of fertilization techniques: patients using donor eggs/embryos, patients using their own eggs with prior ART, and patients with no prior ART using their own eggs. As this technology is expensive and carries some inherent risk to the patient efficiency, for the sake of this analysis is defined by the expected number of reproductive cycles to obtain the desired result of a pregnancy carried to term and ultimately the live birth of at least one healthy child. Within the context of ART efficiency, the most successful demographic was those that had no prior ART using their own eggs when accounting for all procedures. Furthermore, patients who used fresh embryos and frozen eggs, donated embryos, and <35 years of age minimized the number of cycles required for ART success on average. At a higher level of abstraction, the states with the highest level of success on average were all located in the Midwest. Additionally, despite requiring more ART cycles the highest success rate was found among those who used fresh embryos and fresh eggs sourced from a donor. The peak efficiency number of expected cycles appears to remain consistent year to year and there has been a sharp increase in the number of cycles completed by the most recent data.

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INTRODUCTION

Birth rates in modern developed countries are on a net decline, and the United States is no different. Declining birth rates throwing the birth-to-death ratio out of balance would result in a snowball effect of consequences culminating in a reduction in productivity to support aging population as they enter their senior years serving as a defacto senicide. Adults are having children at a later age than ever before and as such it presents an issue of impregnation difficulty as well as bringing children to term. Assisted Reproductive Technology (ART) serves as a possible solution, or at the very least a stop gap in supporting the declining birth rates closer to equilibrium.

As a relatively new technology it's important to analyze the existing data to find trends among successful programs. A variety of patient characteristics are considered to determine which form of ART to pursue. The process of artificial reproduction is time-consuming, expensive, and emotionally draining. Therefore, individuals require the most up-to-date and valuable information in undergoing this treatment because of their limited resources.

With this analysis I hope to define the characteristics for the highest success rates within relevant demographics, the populations most likely to engage in ART, to better educate those engaging in such efforts. Additionally, I would like to find the regions with the highest success rates to develop theories based on the contrasting efforts between clinics to identify what best practices may be.

RELATED WORK:

ART has been a popular topic in biomedical science as the threat of declining birth rates becomes more real. With the development of technology and in science there have been enough procedures to provide a reasonable sample size to perform analysis on the short- and long-term effects of ART.

The most common complication to occur during ART is in the event of multiple pregnancy which can result in health complications for the mother. Furthermore, there has been a link between some variables in perinatal outcomes such as cerebral palsy, autism, neurological developmental imprinting disorders, and cancer. [1]

However, multiple pregnancy complications can be prevented or minimized by the reduction of the number of embryos transferred to the uterus. Additionally, the perinatal adverse outcomes have do not have a certain causal relationship to the procedure itself and it is uncertain whether the general factors that play a role in the development of such disorders in any pregnancy are at work or if there is a pathological link from the procedure.[1]

Of the studies that have been completed so far, and after controlling known risk factors like multiple gestation and preterm delivery the data suggests ART is a safe procedure for patients that choose to go that route.

Artificial Intelligence (AI) has seen integration at every level of society and has been seen as a proposed success multiplier for ART. Although AI holds the potential to enhance ART success there are significant challenges in applying it in clinical applications and outcome-driven validating scenarios.[2]

Currently, AI has too many limitations to provide the exponential impact that the hype around it promises. Some of these limitations are based on ethical concerns with medical data, limited transparency, and regulatory obstacles that severely hinder the development of AI integration.

Despite limitations there has been some headway made in addressing inefficiencies within workflows,

decision making, and advanced image analysis that have improved ART applications.

AI continues to offer potentially promising advances, but like in many fields, it will require significant validation as well as energy improvements to sustainably deliver results. [2]

TECHNIQUES APPLIED:

- Data Cleaning
- Data Integration
- Data Transformation
- Data Selection
- Data Mining
- Pattern Evaluation
- Knowledge Presentation

This work will be different from previous studies because it will focus on homing in on the specific characteristics that lead to the highest probable chance of a successful ART pregnancy as opposed to evaluating the safety of the procedure. Considering the current literature focuses primarily on the safety of the procedure, and validated it to an extent, I will be focusing on how to best achieve the desired result of participants.

DATASETS:

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DATASET DETAILS:

These datasets are a part of the Center for Disease Control (CDC) online database and have been gathered via the National ART Surveillance System (NASS) initiative that collects success rates, and data on ART within the United States.

These datasets are geographically separated by states as well as by patient demographic to include details of

the type of procedure they are engaging in. Some of the relevant attributes within this dataset include, age, attempt number, type of ART, and clinic where it was performed to include the clinic physician performing it.

EVALUATION METHODS:

The results of this analysis will be evaluated by comparing the success rates of the highest performing attributes with the average success rate of all demographics with the intention of being able to determine how successful the best specific patient demographics are in comparison to the worst performing patient demographics and the average success rate across the entire population. I will be able to identify a spectrum of successful characteristics based on patient details. Additionally, I will be able to define which regions are having the greatest success for further evaluation of their programs.

TOOLS:

- Python
- Pandas
- Seaborn
- Numpy

RESULTS:

Analyzing mean ART success by year and region yielded inconclusive results. There was a sharp dip in mean success rate across all regions from 2020 to 2021, 27-30% mean success. Mean success rates hit a low range of 19-21% mean success rate in 2021 before rebounding to 29-30% mean success rate. A possible cause for this trend is likely COVID-19. With a reduction in elective procedures, individuals were willing to participate, and the overall reduction in procedures likely skewed the data. While further analysis needs to be done, the return to higher success rates after 2021 indicate there isn't a significant change for ART success that can be attributed to patient or procedural improvements. Further analysis needs to be done, but for now it is reasonable to conclude that 2021 is an outlier in the data.

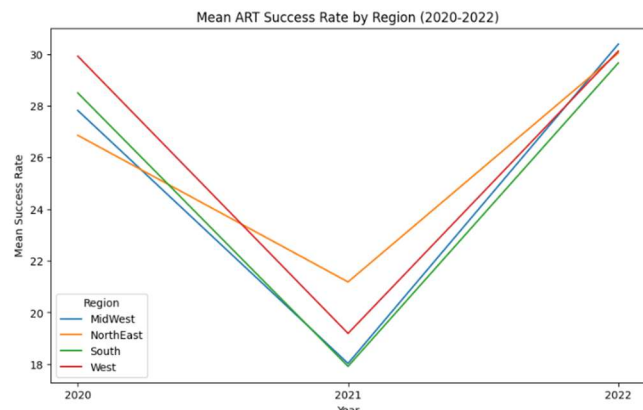


Figure 1: Mean ART Success rate by geographical region from 2020-2022

An interesting finding to note is that within the datasets some more remote states were removed from the analysis if they provided less than 10 instances of statistically significant ART procedural information. Many clinics were doing such low numbers of ART procedures that their results were suppressed within the dataset. Clinics who reported sample sizes of 1-4 for any demographic were suppressed within the data. Additionally, if no reproductive cycles fit the demographic they were also suppressed. All suppressed data entries were removed from the data analysis.

The range of mean ART success percentages are relatively similar across regions for any given year. This finding was surprising in the sense that I expected some wealthier geographical regions to have a higher success rate percentage than some less fortuitous areas. Specifically, I expected the South to have the lowest success rate percentage and the West to have the highest success rate. Figures 2-4 show there wasn't a significant difference between regional success, but the West and South were most successful until other regions closed the gap.

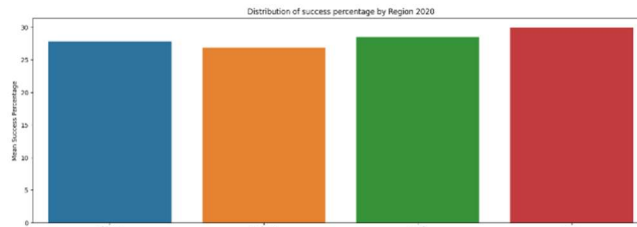


Figure 2: Mean ART Success rate by geographical region 2020

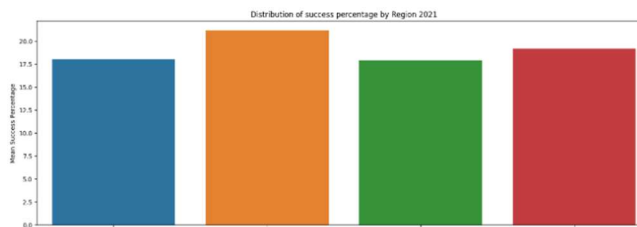


Figure 3: Mean ART Success rate by geographical region 2021

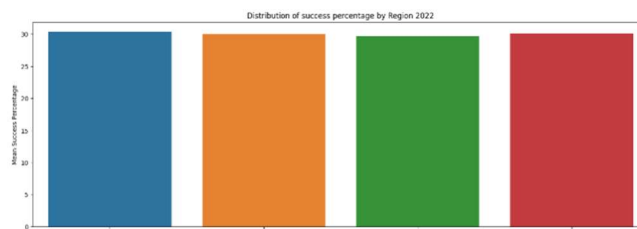


Figure 4: Mean ART Success rate by geographical region 2022

Before filtering for statistically insignificant entries, states and clinics who had less than 10 suppressed entries the counts for state by year were:

2020 Original State Count: 50

2020 Filtered State Count: 40

2021 Original State Count: 47

2021 Filtered State Count: 44

2022 Original State Count: 43

2022 Filtered State Count: 36

This finding poses an interesting question: Why did both the number of ART clinics decline year after year and the number of ART clinics performing enough procedures to be statistically relevant also decline?

Given the decline of the number of procedures it casts a shadow on the idea of ART saving the declining birth rate and maintaining the birth-to death ratio. A causal explanation is yet to be found, but one of the likeliest causes is based on economics. Considering ART is costly, and the economy needed time to recover after COVID-19 it is likely cost played a major role in the amount of procedures done. In reference to the intent of this analysis it adds in the question on how to reduce the costs of ART. At some point the declining birth rate will need to become enough of an issue for government intervention as ART costs on average cost \$12,400 not to include additional medical expenses for birthing. The cost of ART is further defined by the number of cycles to give birth as more cycles equal more expenses. [3]

Figure 5 references 3 specific types of ART procedures: patients using donor eggs/embryos, patients using their own eggs, and patients with no prior ART using their own eggs. This preliminary analysis shows a clear performance indicator for patients using donor eggs/embryos. In all 3 years patients using donor eggs/embryos far surpassed the other two forms of ART which makes sense considering the reason for undergoing the procedure being based on infertility. Those engaging in artificial reproduction by nature have difficulty reproducing on their own so it makes sense that the patients using their own eggs would be less likely to be successful in bringing an embryo to term.

Interestingly, the difference between patients using their own eggs and patients with no prior ART using their own eggs are more different than expected. It is likely more expensive to use a donor egg/embryo and if cost is a major barrier for ART, it is important to analyze the difference in outcome between these two populations. In 2020 patients using their own eggs with prior ART experience outperformed patients

with no prior experience. 2021 saw the trend continue with patients with prior ART experience using their own eggs being more successful than those without prior experience using their own eggs. However, in 2022 despite both populations seeing an increase in success those with no prior experience outperformed those with prior experience.

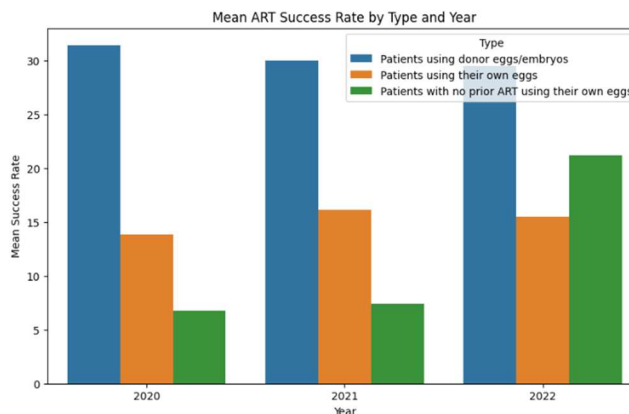


Figure 5: Mean ART Success Rate by Type and Year 2020- 2022

These results drove the intermediate analysis by separating the patients that use donor eggs/embryos into their own category to further analyze and define the most successful attribute within the most successful category. Additionally, delving into the patients that don't use donor eggs/embryos helped determine what characteristics lend to greater success for those unable or unwilling to use a donor whether for cost or personal preference.

Further analysis required the calculation of an efficiency metric considering the cost of ART as the largest barrier to treatment. The expected number of cycles required to result in a live birth was calculated using the existing success percentage presented in the data.

Efficiency = $1 / \text{ART success percentage}$

In 2020 and 2021 the top performing ART clinic was the Advanced Fertility Center of Chicago located in Illinois and operated by Michelle Catenacci, MD. The minimum number of reproductive cycles required for successful live birth were ~1.05 for 2020 and ~1.08 for 2021. The peak reproduction efficiency seen in

2020 was achieved primarily with patients using a donor with fresh embryos and fresh eggs. 2021 saw a shift in methodology used to achieve peak results to patients using their own eggs and were under the age of 35. In 2022 the top performing clinic was the Fertility Center of Southern California ran by medical director Ilene E. Hatch, MD and were able to achieve a peak efficiency rate of ~ 1.04 expected cycles to result in a live birth. This most recent peak saw another shift in methodology where patients used donor eggs like in 2020, but the embryos were frozen.

The shift in the techniques used to achieve the least expected number of cycles is interesting considering the worst performing attributes within each year. In 2020 the 10 least efficient cycles, requiring the most number of reproductive cycles to result in a live-birth, were within the categories of patients using their own eggs between the ages of 35-40. The worst performing demographics in 2021 were patients ~ 40 years old that used their own eggs. Considering the peak efficiency rate was achieved this year with patients <35 years old using their own eggs the age of the gestational carrier appears to play a large factor in ART success. 2022 saw a shift in poorest performing demographics once more to patients that used donor eggs and embryos that were previously frozen.

The drastic shifts in efficiency attributes highlights the newness of the technology as the stark changes in peak-performing demographics could possibly be due to the refinement of processes.

The best performing states followed the same pattern as the peak single performing clinics as expected. With the top-performing clinics likely weighting the overall state average, the best performing state in 2020 and 2021 was Illinois. In 2022 the best performing states were California and Massachusetts.

In contrast the worst performing states were located in the Northeast United States in 2020, then shifted to the West Coast with California and Colorado among the most frequent worst performing clinics in 2021. In 2022 the worst performing clinics were spread out and didn't have a regional pattern to them.

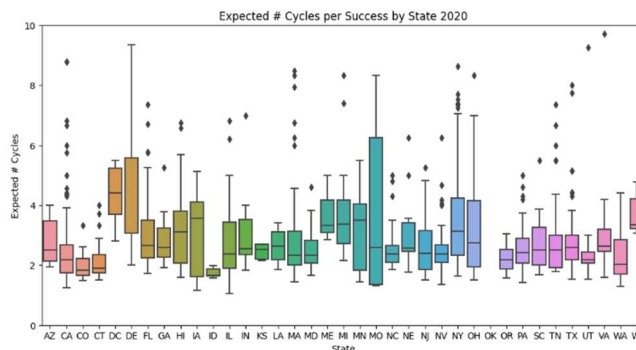


Figure 6: Expected number of cycles required to result in a live birth by state in 2020

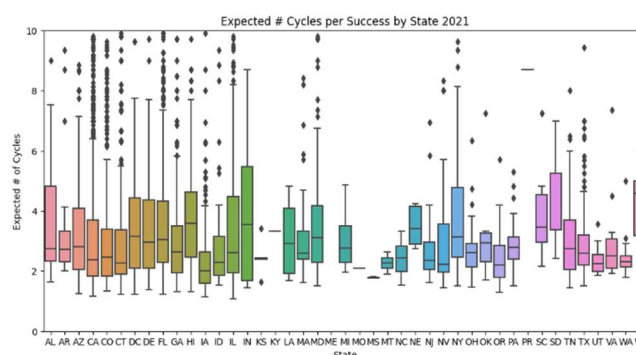


Figure 7: Expected number of cycles required to result in a live birth by state in 2021

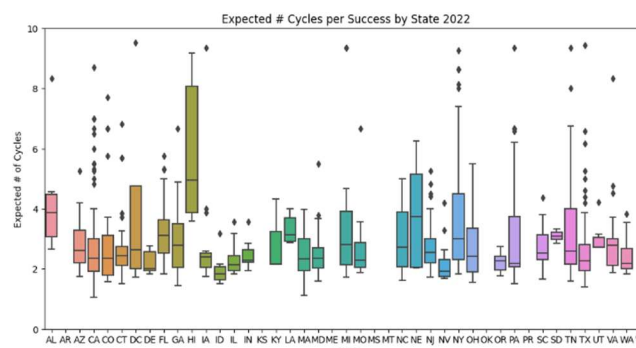


Figure 8: Expected number of cycles required to result in a live birth by state in 2022

Acute examination shows variation in methodology with the best results but the peak efficiency of the best clinics lends itself to individuals with the means to access the full spectrum of ART options.

Unfortunately, the prospect of the best available methodologies at the best clinics having dramatically better efficiency rates does not address the issue of declining birth rates as the affluent by nature are a small percentage of the population in the United States.

To grasp the best attributes and expected outcomes for most of the population the mean points to how viable ART is in supplementing the birth rate in the United States. In 2020, the best performing state across all clinics in the state was Kansas. The mean expected number of cycles to achieve a successful childbirth was ~2.46. When compared to the peak 2020 expected number of cycles, the average expected number of cycles more than doubled. The best performing patients used donor eggs and embryos that were frozen.

In 2021 Mississippi led all states in average efficiency with a rate of ~1.78. It's curious to see such a drop in average efficiency from year to year, however it's difficult to frame the relevancy of the 2021 average considering there was a nearly 30% decrease in the number of cycles performed in comparison to the prior year. Patients who used their own eggs and were under the age of 35 saw the best results.

2022 saw Kentucky lead all states in average expected cycles needed for viable offspring with a rate of ~2.89, nearly tripling the peak rate achieved in California. A possible explanation for this large difference can likely be found in the doubling of ART cycles completed in 2020 and triple those done in 2021. Similar to 2020 the highest performing demographic used donor eggs and embryos that were frozen.

2020 Number of ART cycles: 3252883

2021 Number of ART Cycles: 2514131

2022 Number of ART Cycles: 7228336

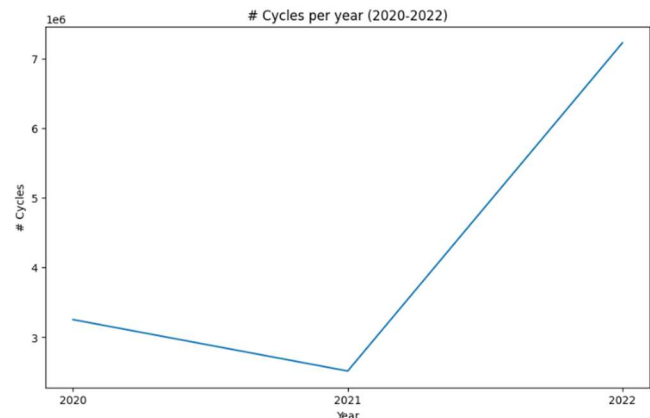


Figure 9: Number of ART Cycles per year

For those located outside of the highest performing states the national average is a better estimate of how many cycles they can expect for successful reproduction. From 2020-2022 patients with no prior ART using their own eggs saw the best results with an average expected number of cycles ~3.62. There wasn't a clear distinction of what additional factors added to mean patient success, but the top three performing additional demographics were in order of year 2020-2022: fresh embryos and frozen eggs, donated embryos, and age <35.

APPLICATIONS:

This analysis can be used to help guide patients considering or even currently undergoing ART to best plan their fertilization journey as well as provide a projection to future changes.

Patients who have the means to seek out the best clinics can see how much more efficient their process can be at the best performing clinics. This information is especially important for this demographic as time is one of the only things money can't buy.

Those located in the best performing states on average can also use this information to guide their plan of care by selecting the best performing attributes to ART success for their state.

For patients who aren't located in the top performing areas they can look to the national average best attributes for guidance as to which forms of ART to explore with their physician to optimize their success.

Lastly, this information can be used to project the future changes in ART. As the number of cycles increases overtime the data becomes more reliable and will do a better job of describing optimal conditions for successful ART. Additionally, if a patient can't make use of the best performing attributes, they can determine what the next best option is, or at least how different the expectations are from the optimal scenario.

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