

Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss

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Objective: To determine whether in vitro fertilization with preimplantation genetic screening (IVF/PGS) is cost effective compared with expectant management in achieving live birth for patients with unexplained recurrent pregnancy loss (RPL).

Design: Decision analytic model comparing costs and clinical outcomes.

Setting: Academic recurrent pregnancy loss programs.

Patient(s): Women with unexplained RPL.

Intervention(s): IVF/PGS with 24-chromosome screening and expectant management.

Main Outcomes Measure(s): Cost per live birth.

Result(s): The IVF/PGS strategy had a live-birth rate of 53% and a clinical miscarriage rate of 7%. Expectant management had a live-birth rate of 67% and clinical miscarriage rate of 24%. The IVF/PGS strategy was 100-fold more expensive, costing \$45,300 per live birth compared with \$418 per live birth with expectant management.

Conclusion(s): In this model, IVF/PGS was not a cost-effective strategy for increasing live birth. Furthermore, the live-birth rate with IVF/PGS needs to be 91% to be cost effective compared with expectant management. (Fertil Steril® 2015; ■: ■-■. ©2015 by American Society for Reproductive Medicine.)

Key Words: Cost effectiveness, in vitro fertilization, preimplantation genetic screening, recurrent pregnancy loss

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Recurrent pregnancy loss (RPL) is a multifactorial disorder defined by two or more clinical miscarriages (1). Although the overall incidence of RPL is low and estimated at less than 5% of women (2), it presents a significant diagnostic and treatment challenge for both patients and clini-

cians. Guidelines for the evaluation of patients with RPL include evaluation of the uterine cavity and blood work to determine parental karyotypes and presence of antiphospholipid antibodies (1). An etiology for RPL, however, is not identified in at least 50% of cases, and a treatment plan is thus not

clearly defined (3). The role of chromosomal abnormalities in miscarriage has been widely reported, with 50% to 70% of first trimester miscarriages attributed to aneuploidy (4, 5). Furthermore, for patients greater than 35 years of age with RPL, fetal aneuploidy is responsible for up to 80% of first trimester losses (6). Due to the prevalence of aneuploidy in first trimester losses and the increased prevalence of aneuploidy in the RPL population, preimplantation genetic screening (PGS) has been proposed as a method for reducing miscarriage by

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selecting euploid embryos for transfer. The current standard of care for patients with unexplained RPL espoused by the American Society for Reproductive Medicine is expectant management (1, 7). However, the emotional trauma that can accompany clinical miscarriages and a perceived urgency to conceive felt by many RPL patients lead them toward alternative treatment options, including assisted reproductive technology, and specifically to in vitro fertilization (IVF) and PGS (8).

The clinical outcomes and cost effectiveness of PGS and IVF in the treatment of RPL patients is uncertain. Neither longitudinal prospective studies nor randomized clinical trials comparing IVF and PGS with expectant management, the current standard of care, have been performed to date for the treatment of RPL patients. Furthermore, IVF and PGS are technically challenging, resource-intensive procedures that are expensive and not widely available (9). We used the current literature to evaluate the cost effectiveness of IVF and PGS compared with expectant management in patients with unexplained RPL.

MATERIALS AND METHODS

A decision analytic model was created using TreeAge Pro 2014 (2014 version; TreeAge Software) to compare the cost effectiveness of IVF-PGS versus expectant management for patients with unexplained RPL (Fig. 1). As no human participants were involved in creating this theoretical model, this study was exempt from institutional review board approval. Two treatment strategies were compared: IVF-PGS versus expectant management.

In the IVF-PGS strategy, patients underwent one IVF cycle followed by PGS and fresh embryo transfer if a euploid

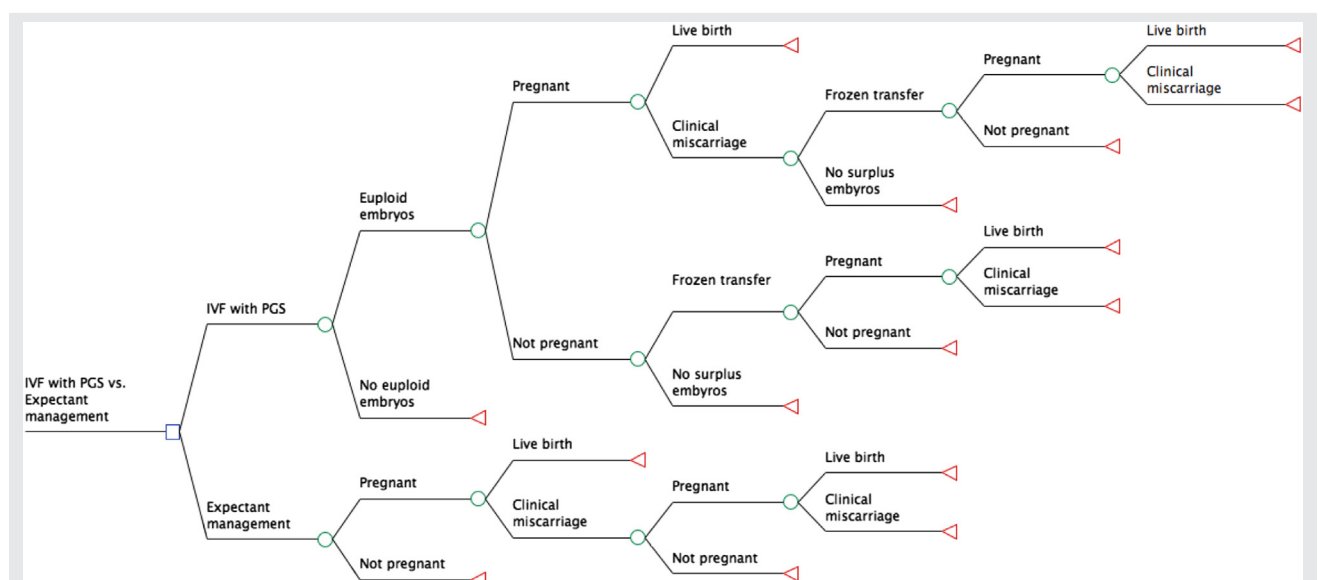
embryo was produced. After embryo transfer, the possible outcomes included pregnancy followed by live birth, or clinical miscarriage, or no pregnancy. Patients who had a clinical miscarriage or did not become pregnant after the first embryo transfer were allowed to attempt a frozen embryo transfer if they had surplus embryos. In the expectant management strategy, patients attempted spontaneous conception. Possible outcomes included pregnancy followed by live birth, or clinical miscarriage, or no pregnancy. Patients who had a clinical miscarriage after their first attempt were allowed a second attempt at conceiving spontaneously. Patients were randomly assigned to the two treatment strategies, and the baseline clinical outcomes for each strategy were obtained from published data.

We assumed that no patients dropped out between their first and second attempts at either strategy, and we also assumed that baseline clinical outcomes were unchanged between the first and second attempts at either strategy. In the IVF-PGS strategy, we assumed that transfers were only performed if at least one euploid embryo was produced, and that a second attempt at IVF-PGS with a frozen transfer was only performed if at least one surplus euploid embryo was present upon completion of the fresh transfer.

No ectopic or cervical pregnancies were present in either patient cohort, so all pregnancies ended in either live birth or clinical miscarriage. Clinical pregnancy and live-birth rates calculated from the analytic model are expressed per strategy, and clinical miscarriage rates are expressed per pregnancy.

Probabilities for clinical outcomes with IVF and PGS in RPL patients were obtained from a 2012 study by Hodes-Wertz et al. (10). This is the single largest study to date of outcomes using 24-chromosome screening by array comparative genomic hybridization in a well-defined RPL population.

FIGURE 1



Simplified decision tree. Patients with unexplained recurrent pregnancy loss were assigned to one of two treatment strategies: expectant management or in vitro fertilization (IVF) with preimplantation genetic screening (PGS).

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Probabilities for outcomes with expectant management were obtained from a landmark study by Brigham et al. (11) from 1999, which is the most commonly cited, single largest observational study of expectant management in RPL patients.

In both studies, RPL was defined as greater than or equal to or two clinical miscarriages between 6 and 20 weeks' gestational age. Biochemical pregnancies and intrauterine fetal demise beyond 20 weeks gestation were not included as clinical miscarriages. In both studies, only patients with unexplained RPL were included. Unexplained RPL was defined as patients with at least two prior unexplained clinical miscarriages, normal anatomy of the uterine cavity, negative antiphospholipid antibody syndrome testing, and normal parental karyotypes. Hodes-Wertz et al. (10) also excluded patients with endocrine disorders and translocation carriers. Brigham et al. (11) also excluded patients with oligomenorrhea, cervical weakness, and patients with abnormal karyotypes.

In both studies, a clinical pregnancy was defined as the presence of an intrauterine gestational sac as documented by ultrasound. An ongoing pregnancy was defined as a pregnancy past the second trimester, and a clinical miscarriage was defined as pregnancy loss at less than 20 weeks' gestational age. Live birth was defined as birth of an infant beyond 24 weeks' gestational age (10, 11).

The Hodes-Wertz study reported on outcomes of 287 cycles of IVF with 24-chromosome PGS with a total of 2,282 embryos followed by fresh day-5 embryo transfer in RPL patients. Of the PGS cycles, 67% were biopsied on day 3, and 33% were biopsied on day 5. The average maternal age was 36.7 years (range: 21–45 years), and the mean number of prior miscarriages was 3.3 (range: 2–7). From 287 PGS cycles, 181 cycles had at least one euploid embryo and proceeded to fresh embryo transfer. There were 52 cycles with no euploid embryos for transfer, four cycles where an embryo transfer had not taken place at the time of analysis, and 51 cycles that were lost to follow-up observation. All patients with a euploid embryo proceeded to embryo transfer, with an average of 1.65 ± 0.65 (range: 1–4) embryos per transfer.

Excluding the cycles lost to follow-up evaluation and the cycles without a transfer at the time of analysis, the clinical pregnancy rate per attempt was 44% (n = 102). One attempt at conception was defined as an IVF cycle and oocyte retrieval ± embryo transfer. The live-birth rate per attempt was 40% (n = 94), and the miscarriage rate per pregnancy was 7% (n = 7). Of these seven miscarriages, 57% (n = 4) occurred after detection of fetal cardiac activity (10). Information on the percentage of cycles with surplus embryos was not provided in the Hodes-Wertz study, so we drew from their database of 240 RPL patients with 118 attempts at IVF and PGS (12). The clinical pregnancy, live-birth, and clinical miscarriage rates did not statistically significantly differ between the outcomes published in the Hodes-Wertz study ($P = .89$, $P = .66$, $P = .61$, respectively). We reported that 62% of IVF cycles had at least one surplus embryo (12).

Probabilities for expectant management were obtained from a prospective longitudinal study by Brigham et al. (11) of 325 patients with unexplained RPL who underwent initial clinical evaluation and attempted spontaneous conception

with close interval follow-up observation. The average maternal age was 32 years (range: 17–45 years), and the mean number of prior miscarriages was 3 (range: 2–10). Excluding cycles lost to follow-up observation, the clinical pregnancy rate was 75% (n = 226), and the live-birth rate was 55% (n = 167). The clinical miscarriage rate per pregnancy was 24% (n = 55). Miscarriages were divided into first trimester losses, which accounted for 98% of miscarriages (n = 54), and second trimester losses, which accounted for 2% of miscarriages (n = 1). Of the clinical miscarriages, 3% (n = 6) occurred after the detection of fetal cardiac activity (11).

The time to conception with expectant management or IVF-PGS was not provided by either study, so we were unable to input this in our model. A comparison of baseline clinical probabilities between the IVF-PGS and expectant management groups obtained from the literature is shown in Table 1 (10, 11).

Cost data were obtained from the literature and adjusted to 2014 U.S. dollars using the Consumer Price Index (9, 13–15). Only direct medical costs were included. The average cost of preconception counseling and baseline RPL workup, including parental karyotyping, maternal antiphospholipid antibody testing, and uterine cavity evaluation, was \$4,377 (range: \$4,000–\$5,000) (16). Because this was incurred by both groups before their entry into the decision tree, it was not included as a cost input in the study. The average cost of IVF was \$18,227 (range: \$6,920–\$27,685) (16) and includes cycle medications, oocyte retrieval, and one embryo transfer. The average cost of PGS was \$4,268 (range \$3,155–\$12,626) (17), and the average cost of a frozen embryo transfer was \$6,395 (range: \$3,155–\$12,626) (13, 16). The average cost of managing a clinical miscarriage with dilation and curettage (D&C) was \$1,304 (range: \$517–\$2,058) (18). Costs incurred in the IVF-PGS strategy include the cost of IVF, PGS, fresh embryo transfer, frozen embryo transfer, and D&C. Costs incurred in the expectant management strategy include only the cost of D&C.

The cost to achieve one live birth was the primary outcome of the analysis. The cost to prevent one clinical miscarriage was the secondary outcome of the analysis. Cost effectiveness was defined as an incremental cost-effectiveness ratio (ICER). This was derived from previously

TABLE 1

Baseline clinical probabilities from the literature: IVF-PGS versus expectant management.

Parameter	IVF-PGS (n = 232) ^a	Expectant management (n = 302) ^b
Pregnancy rate (% , n)	44 (102) ^c	75 (226)
Live-birth rate (% , n)	40 (94) ^c	55 (167)
CM rate (% , n)	7 (7) ^d	24 (55) ^d

Note: CM = clinical miscarriage; IVF-PGS = in vitro fertilization with preimplantation genetic screening.

^a Obtained from Hodes-Wertz et al. 2012 (10).

^b Obtained from Brigham et al. 1999 (11).

^c Calculated per attempt, which was defined as an IVF cycle and oocyte retrieval ± embryo transfer.

^d Calculated per pregnancy.

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published analyses, where a threshold of less than \$100,000/QALY (quality-adjusted life year) was used to determine cost effectiveness (19, 20). The ICER for live birth was calculated as the difference in cost between the treatment strategies divided by the difference in live-birth rates between the treatment strategies. The threshold for cost effectiveness was defined as an ICER of less than \$100,000 per additional live birth. Base case, threshold, and sensitivity analyses were performed to assess the robustness of the model.

RESULTS

Compared with expectant management, the IVF-PGS strategy was more expensive, had a lower live-birth rate, and had a lower clinical miscarriage rate (Table 2). The clinical pregnancy rate per strategy was 88% for expectant management, compared with 56% for IVF-PGS. The live-birth rate per strategy was 67% for expectant management compared with 53% for IVF-PGS. We found that IVF-PGS was 100-fold more expensive than expectant management, costing \$45,300 per live birth, compared with \$418 per live birth with expectant management.

The IVF-PGS strategy cannot be cost effective compared with expectant management because it has a lower live-birth rate and higher cost. The IVF-PGS strategy does have a lower clinical miscarriage rate than expectant management, so it is possible for IVF-PGS to be cost effective for averting clinical miscarriage. The cost per clinical miscarriage averted with IVF-PGS is \$135,054, which is above the cost effectiveness threshold of \$100,000. From this base case analysis, IVF-PGS is not cost effective compared with expectant management for either primary or secondary outcomes of the model.

A series of sensitivity analyses were performed to optimize the cost effectiveness of IVF-PGS. First, the clinical miscarriage rate of IVF-PGS was set at 0 to model a hypothetical corner case, or the best possible miscarriage rate, while the clinical miscarriage rate of expectant management was held at the baseline of 24%. Even in this simulated scenario, expectant management was the dominant strategy compared with IVF-PGS, as it continued to be less expensive and more effective. The live-birth rate was 56% for IVF-PGS and 67% for expectant management, and the cost per live birth was \$42,568 for IVF-PGS compared with \$418 for expectant management.

A second sensitivity analysis was performed looking at the alternative corner case in which the live-birth rate of IVF-PGS was 100%, or the best possible live-birth rate, while the live-birth rate of expectant management was held at the baseline of 67%. The cost of IVF-PGS in this analysis was \$24,009, and the cost of expectant management was \$280. In this simulated scenario, an ICER can be calculated because IVF-PGS has a higher live-birth rate than expectant management, although it is the more expensive strategy. The incremental cost per additional live birth with IVF-PGS compared with expectant management was \$71,906. Additionally, the lowest possible live-birth rate of IVF-PGS for this strategy to be cost effective compared with expectant management is 91%. At a live-birth rate of 91% for IVF-PGS, the incremental cost per additional live birth is \$100,000 compared with expectant management.

A two-way sensitivity analysis was also performed to compare the treatment strategies. Two different parameters of the IVF-PGS strategy were optimized: the pregnancy rate of IVF-PGS was set to 100%, and the percentage of cycles with surplus embryos was set to 100% while the pregnancy rate of expectant management was held at the baseline of 88%. From this analysis, the live-birth rate with IVF-PGS was 77%, and the live-birth rate with expectant management was 67%. The incremental cost per additional live birth with IVF-PGS compared with expectant management was over \$200,000.

A one-way threshold analysis was then performed on clinical miscarriage rates to investigate the effect, if any, of maternal age on selecting the cost-effective treatment strategy. Age is an important predictor of success with both IVF-PGS and expectant management. The average maternal age was higher in the Hodes-Wertz cohort compared with the Brigham cohort (36.7 versus 32 years of age, respectively). Hodes-Wertz et al. (10) stated that there was no statistically significant difference in clinical pregnancy rate between patients <35 years of age and ≥35 years of age once embryo transfer is reached, but age-stratified clinical pregnancy and clinical miscarriage rates were not provided in their study. In the Brigham study (11), clinical outcomes across age groups were calculated by a logistic regression model. Women 35 years of age with two prior clinical miscarriages had a 77% predicted live-birth rate (CI, 69%–85%) compared with 60% (CI 41%–79%) for women 45 years of age with expectant management. The highest clinical miscarriage rate calculated by the Brigham study in a patient >45 years of age with five prior clinical miscarriages was 58%.

Using the assumption that the clinical miscarriage rate increases with maternal age, we fixed the clinical miscarriage rate of IVF-PGS at the baseline of 7% and varied the clinical miscarriage rate of expectant management from 0 to 100%. From this analysis, we identified the clinical miscarriage rate at which IVF-PGS becomes cost effective compared to expectant management. We then sought to determine whether this miscarriage rate was clinically relevant, which would suggest that the difference in maternal age between the cohorts influenced the results of our analysis. In this threshold analysis, IVF/PGS was the cost-effective strategy when the clinical miscarriage rate for expectant management

TABLE 2

Base case analysis: cost outcomes at 7% clinical management rate for IVF-PGS.

Parameter	IVF-PGS	Expectant management
Cost	\$24,009	\$280
Live-birth rate ^a	53%	67%
CM rate ^b	7%	24%
Cost per live birth	\$45,300	\$418

Note: CM = clinical miscarriage; IVF-PGS = in vitro fertilization with preimplantation genetic screening.

^a Calculated per strategy.

^b Calculated per pregnancy.

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was greater than 74%. This well exceeds the highest predicted clinical miscarriage rate of 58% by the Brigham study and is thus not in a clinically relevant range.

DISCUSSION

Presently, IVF-PGS is increasingly used for RPL patients due to the prevalence of fetal aneuploidy in first trimester clinical miscarriages. The clinical effectiveness of IVF and PGS compared with expectant management, which is the current standard of care in the treatment of RPL patients, has not been investigated with longitudinal prospective studies or randomized clinical trials. Furthermore, IVF-PGS is an expensive treatment option, and the cost effectiveness of IVF-PGS compared with expectant management needs to be investigated.

There are pros and cons to calculating cost effectiveness with the threshold of averting miscarriage or increasing live birth. Our bias is that reducing miscarriage but not increasing live birth misses the primary goal of treatment. Although many patients would rather not miscarry than have a negative pregnancy test, their primary goal of treatment is to have a child. Furthermore, no treatments and no attempts to conceive also result in no miscarriages. Therefore, cost effectiveness was defined in our study in terms of achieving live birth.

We report that when RPL patients treated with IVF and 24-chromosome PGS were compared with patients who were expectantly managed, the IVF-PGS treatment strategy had a lower clinical miscarriage rate, a lower live-birth rate, and was 100-fold more expensive than expectant management. In this model, we report that IVF-PGS is not a cost-effective tool for increasing the number of live births in the RPL population. Both one and two-way sensitivity analyses demonstrated that IVF-PGS becomes the cost-effective strategy compared with expectant management when the live-birth rate of IVF-PGS is at least 91%.

The limitations of our study should be acknowledged. In both studies examined, a small proportion of patients were lost to follow-up observation and were excluded from the analysis. In addition, the live-birth rate reported by Hodes-Wertz et al. (10) is similar to our reported live-birth rate but is lower than outcomes reported by other studies on PGS. It is possible that the IVF-PGS outcomes are worse in RPL patients than in general infertility patients due to gamete or uterine dysfunction that is not identified with aneuploidy screening alone; we cannot assume that RPL patients will do as well as other patients with this treatment. Additionally, in a population with both infertility and RPL, cost effectiveness analysis would likely show different conclusions. This is outside of the scope of our study.

Time to conception was not provided in either the Hodes-Wertz or Brigham studies, and thus was not a separate model input. However, we looked at time to conception in a separate study. In 2014, Perfetto et al. (2014, unpublished data) performed a retrospective cohort study of fertile RPL patients and showed that the median time to conception was 2 months for those patients who achieved a spontaneous conception; 88% conceived within 6 months. In comparison, patients using IVF and PGS conceived in a median of 5 months.

Thus, IVF-PGS does not decrease the time to conception compared with expectant management.

The average maternal age was higher in the IVF-PGS patient group compared with the expectant management group. A one-way threshold analysis identified that when the clinical miscarriage rate of expectant management exceeds 74%, IVF-PGS becomes the cost-effective treatment strategy. Because this miscarriage rate is not in a clinically relevant range, we were unable to identify a subset of RPL patients who will benefit from IVF-PGS as a cost-effective strategy for increasing live birth, regardless of maternal age. With new advances in PGS technologies such as the addition of day 5–6 biopsy and frozen embryo transfer, we may be able to see higher live-birth rates with IVF-PGS, but this strategy adds cost, and we think it is unlikely to have a major impact on cost effectiveness. These strategies are also unlikely to reduce the miscarriage rate, and they likely will increase the time to pregnancy. Further prospective studies are warranted to clarify this analysis.

Obstetric costs were not included in this analysis, nor were adjustments made for the higher rates of multiple births and obstetric complications after IVF-PGS. An average of 1.65 ± 0.65 (range: 1–4) embryos were transferred in the IVF-PGS group. In a study comparing outcomes of single-versus two-embryo transfers after IVF, there was a statistically significant difference in the number of multiple births (1.6% with single-embryo transfer and 47% with two-embryo transfer) with a statistically significantly higher rate of preterm delivery, low birth weight, and neonatal intensive care unit admission associated with two-embryo transfers (21). The societal and financial cost of the multiple gestations associated with IVF is thus important to incorporate in future cost analyses, and it is likely to skew the results further in favor of expectant management.

The primary outcome of our cost-effectiveness analysis was the cost per live birth. An alternative is to express the results as cost per QALY, or quality-adjusted life year. This allows use of the QALY as a comparable denominator across studies and incorporates factors outside of financial cost that patients may experience (22). The literature on IVF and RPL acknowledges but does not yet quantify non-monetary costs, and it is our hope that these will continue to be investigated and can be incorporated into future cost-effectiveness analyses.

Given the emotional distress of RPL, the most important job of the provider is to provide evidence-based advice and counseling to patients in the context of their goals and priorities. It is often unsettling for a patient who has experienced multiple pregnancy losses to try again with no intervention, and the temptation to undergo invasive treatments is often great. When live birth is the primary goal, patients must be counseled on the chances of conceiving as well as carrying to term with each treatment option, not just the risk of miscarriage.

Given the current literature, it appears that IVF-PGS is a very costly way to reduce miscarriage without increasing the chance of achieving a live birth, so it deserves further study before being recommended as standard treatment for RPL. Well-designed prospective trials that take into account clinical

outcomes, cost, and the patient's experiences with treatment options are needed to better counsel our RPL patients.

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