Economic evaluation of highly purified human menotropin or recombinant follicle-stimulating hormone for controlled ovarian stimulation in high-responder patients: analysis of the Menopur in Gonadotropin-releasing Hormone Antagonist Single Embryo Transfer–High Responder (MEGASET-HR) trial

Jared C. Robins, M.D.,a Andrew F. Khair, Ph.D., M.B.A.,b Eric A. Widra, M.D.,c Michael M. Alper, M.D.,d Winnie W. Nelson, Pharm.D., M.S., M.B.A.,b Eric D. Foster, Ph.D.,b Anshul Sinha, B.Tech.,b Masakazu Ando, Ph.D.,b Patrick W. Heiser, Ph.D.,b and Gaurang S. Daftary, M.D., M.B.A. b

a Northwestern University, Chicago, Illinois; b Ferring Pharmaceuticals, Inc., Parsippany, New Jersey; c Shady Grove Fertility, Rockville, Maryland; and d Boston IVF, Waltham, Massachusetts

Objective: To determine the cost of achieving a live birth after first transfer using highly purified human menotropin (HP-hMG) or recombinant follicle-stimulating hormone (FSH) for controlled ovarian stimulation in predicted high-responder patients in the Menopur in Gonadotropin-releasing hormone Antagonist Single Embryo Transfer–High Responder (MEGASET-HR) trial.

Design: Cost minimization analysis of trial results.

Setting: Thirty-one fertility centers.

Patient(s): Six hundred and nineteen women with serum antimüllerian hormone ≥5 ng/mL.

Intervention(s): Controlled ovarian stimulation with HP-hMG or recombinant FSH in a gonadotropin-releasing hormone (GnRH) antagonist assisted reproduction cycle where fresh transfer of a single blastocyst was performed unless ovarian response was excessive whereupon all embryos were cryopreserved and patients could undergo subsequent frozen blastocyst transfer within 6 months of randomization.

Main Outcome Measure(s): Mean cost of achieving live birth after first transfer (fresh or frozen).

Result(s): First-transfer efficacy, defined as live birth after first fresh or frozen transfer, was 54.5% for HP-hMG and 48.0% for recombinant FSH (difference 6.5%). Average cost to achieve a live birth after first transfer (fresh or frozen) was lower with HP-hMG compared with recombinant FSH. For fresh transfers, the cost was lower with HP-hMG compared with recombinant FSH. The average cost to achieve a live birth after first frozen transfer was also lower in patients treated with HP-hMG compared with recombinant FSH.
Optimal treatment is delivered when there is confluence among the concerns and priorities of the patient, provider, and payer. Patients with infertility are often the payers for such care; addressing the multiple factors that inform treatment decisions thus generates comprehensive medical and financial value. Traditionally, clinical trials have been designed to report treatment success based on efficacy and safety. However, in modern medical decision making, relative efficacy needs to be considered and balanced against practical factors including cost.

Patients and payers (who are often the same in the United States) are key participants in infertility treatment decisions, where cost and patient experience have proven to be barriers that limit pursuit of treatment (1–5). Given a choice, patients with infertility prefer the most effective therapy, particular when it is safe, convenient, and at lower cost. An approach that considers not only efficacy and safety but also economic impact and resource utilization thus allows patients as well as clinicians to make better informed decisions about treatment protocols.

The Menopur in Gonadotropin-releasing Hormone Antagonist Single Embryo Transfer–High Responder (MEGASET-HR) trial was a randomized, open-label, assessor-blind, parallel-group, noninferiority trial of 620 patients conducted at 31 centers across the United States [6]. Patients were randomized to undergo controlled ovarian stimulation in an in vitro fertilization–intracytoplasmic sperm injection (IVF-ICSI) cycle using either highly purified human menotropin (HP-hMG) or recombinant follicle-stimulating hormone (FSH) with a gonadotropin-releasing hormone (GnRH) antagonist for pituitary suppression. Efficacy and safety outcomes were determined after fresh or any frozen transfer of a single blastocyst undertaken up to 6 months from the date of randomization. The trial met its primary noninferiority end point of ongoing pregnancy rate per cycle start after fresh transfer with rates of 35.5% associated with HP-hMG and 30.7% with recombinant FSH treatment (difference 4.7%; 95% CI, −2.7%–12.1%).

Although previous studies comparing the efficacy and safety of HP-hMG with recombinant FSH have been conducted in more homogenous patient populations, the MEGASET-HR trial focused on high responders [7–13]. High-responder patients present an overall good prognosis but also have a higher risk of iatrogenic complications, presenting a challenge in treatment [14, 15]. Previous studies have shown that a “choice of treatment paradigm” has an impact on safety and efficacy in patients considered to be high responders [16–19]. Analysis of MEGASET-HR clinical trial data has provided an opportunity to understand whether gonadotropin choice further impacts the cost of treatment in this patient population.

We conducted a cost minimization analysis using actual costs from the trial sites and medication costs from available cash pricing. By incorporating the economic impact of all procedures and practices that are inherent in any assisted reproductive technology (ART) cycle combined with trial outcomes, we constructed a decision-tree model that enabled determination of the financial impact of therapy per live birth via two distinct stimulation protocols.

**Materials and Methods**

The reporting of this economic evaluation follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [20]. The MEGASET-HR trial is the first randomized controlled comparator trial of the impact of gonadotropin choice on controlled ovarian stimulation in high-responder patients in the United States. The trial was performed across 31 fertility centers between August 2015 and February 2018 and was designed in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable regulatory requirements inclusive of approval by applicable institutional review boards.

Potential high-responder participants with a baseline antimüllerian hormone (AMH) level of >5 ng/mL measured by the central laboratory were included in this trial; this decision was based on results from retrospective analyses of two prior comparative randomized controlled trials that showed that HP-hMG is associated with increased efficacy and safety in subpopulations of patients with a screening AMH level >5.2 ng/mL. Further details of the design of MEGASET-HR were previously described by Witz et al. [6] and Arce et al. [16, 17].

Per study protocol, transfers (fresh or frozen) could be initiated within 6 months of the date of randomization. Pregnancy and live-birth outcomes were collected from all transfers in the post-trial follow-up period. In this trial, freeze-all was only permitted for a risk of ovarian hyperstimulation syndrome necessitating the use of a GnRH agonist trigger in place of human chorionic gonadotropin (hCG) based on the following protocol criteria: >30 follicles of ≥12 mm size and/or a serum estradiol level >5000 pg/mL.

All blastocysts underwent trophectoderm biopsy for PGT-A analysis. Embryo selection was based solely on morphology for fresh transfer, whereas PGT-A results were available at the time of frozen transfer; freeze-all for elevated serum progesterone was not allowed by protocol as previously published.
The primary end point for the original trial was ongoing pregnancy per cycle start in a fresh embryo transfer cycle. This economic analysis was performed from a payer’s perspective. Because the payer is most often the patient in the United States, the focus of this analysis was the cost to achieve a live birth after first transfer, which is the ultimate goal of patients undergoing treatment for infertility. We therefore analyzed first-transfer efficacy, defined as live birth after first fresh or first frozen transfer. The difference in first-transfer efficacy was 6.5% (95% CI, −2.3%–15.4%) indicating noninferiority between the two treatments, which was the rationale for using cost minimization analysis. The MEGASET-HR trial protocol required single-blastocyst transfer because it afforded each patient the best biological opportunity of safely accomplishing a singleton live birth. Patients with other risk factors that could diminish success rates were excluded per trial criteria; the trial achieved its primary noninferiority end point, and the cumulative live-birth rates were comparable in the two treatment arms.

Treatment costs from participating trial sites were collected through a cost survey. An average of all reported treatment costs across responding sites was used to determine the itemized breakdown of cycle related costs (Table 1). Cash-based gonadotropin pricing was derived using an independent online source that compares costs of medications across multiple pharmacies (21). Gonadotropin costs were only used from pharmacies licensed in states where clinical trial sites were located (Table 1).

A decision tree model was generated based on the MEGASET-HR trial protocol that followed a patient’s treatment course through first transfer (Fig. 1) with corresponding efficacy results from the MEGASET-HR trial, which is the ultimate goal of patients undergoing treatment for infertility. We therefore analyzed first-transfer efficacy, defined as live birth after first fresh or first frozen transfer. The difference in first-transfer efficacy was 6.5% (95% CI, −2.3%–15.4%) indicating noninferiority between the two treatments, which was the rationale for using cost minimization analysis. The MEGASET-HR trial protocol required single-blastocyst transfer because it afforded each patient the best biological opportunity of safely accomplishing a singleton live birth. Patients with other risk factors that could diminish success rates were excluded per trial criteria; the trial achieved its primary noninferiority end point, and the cumulative live-birth rates were comparable in the two treatment arms.

For each transfer type, treatment costs were followed for all possible outcomes associated with the transfer: negative pregnancy test, pregnancy loss, or live birth. Only protocol-mandated decisions were modeled, and corresponding treatment costs were used in the model. Participants in the trial were able to initiate frozen transfers up to 6 months after randomization; however, data from frozen transfers outside of those that represented the first transfer for a given patient were excluded from the analysis because the focus of this analysis was based on first-transfer efficacy.

Safety and efficacy results from the MEGASET-HR trial, as well as stimulation results inclusive of average gonadotropin dose, were used as inputs to the model (Table 2). The modified intent-to-treat (mITT) population was defined as all randomized participants who received at least one dose of HP-hMG or recombinant FSH. There was one participant who was randomized to HP-hMG group but withdrew before taking the first dose because she was found to be pregnant; this patient did not take any dose of HP-hMG or recombinant FSH, so she was excluded from the mITT analysis. This analysis accounts for costs associated with all mITT patients regardless of outcome.

Pharmacoconomics can be studied using several approaches such as cost-benefit, cost-effectiveness, cost-utility, and cost-minimization analysis among others (22). As explained earlier, because first-transfer efficacy was found to be noninferior between the two treatment groups, cost minimization was thus selected as the most suitable analytic methodology for this economic analysis. Cost-minimization analysis of a prospective randomized clinical trial has been previously used to determine the cost of achieving pregnancy with different gonadotropin preparations in a European economic analysis (23).

Mean and standard deviation were used to describe continuous data. The number of patients with an event and the corresponding percentage were used to describe categorical data. Two-sided tests using normal approximations with Yates continuity correction were used to compare proportions. For continuous data, confidence intervals (CI) were calculated using the t-distribution, and two-sample two-sided t-tests assuming unequal variances were used to generate P values.

### Table 1: Costs inputted into model.

| Procedure                        | Cost, $  |
|----------------------------------|----------|
| Stimulation cost                 | 4,202    |
| Retrieval and ICSI               | 5,315    |
| Fresh transfer                   | 2,843    |
| Frozen transfer                  | 4,725    |
| Pregnancy test                   | 40       |
| Transvaginal ultrasound to confirm +
  hCG                              | 275      |
| Early pregnancy loss             | 765      |
| OHSS management                  | 788      |
| Low                              | 1,576    |
| Mild                             | 2,364    |
| Moderate/severe                  | 2,364    |
| (per 75 IU)                      |          |
| Pharmacy                         |          |
| HP-hMG                           |          |
| rFSH                             |          |
| 1                                | 77       |
| 2                                | 184      |
| 3                                | 77       |
| 4                                | 77       |
| 5                                | 197      |
| 6                                | 197      |
| 7                                | 77       |
| 8                                | 115 (58) |
| Average (SD)                     | 88 (9)   |
| Median                           | 88       |

Note: Procedure costs were received from select clinical sites. Stimulation costs included physician fees, monitoring, and laboratory fees. Retrieval costs included costs for surgery center use and physician fees. Frozen transfer costs included medication. Early pregnancy loss accounts for the cost of one additional office visit. Costs for managing OHSS were derived from Csokmay et al (33). Medication costs of gonadotropins were obtained an independent online source that compares costs of medications across multiple pharmacies (21). ICSI = intracytoplasmic sperm injection; OHSS = ovarian hyperstimulation syndrome; SD = standard deviation.

Robins. HP-hMG therapy lowers cost to live birth. Fertil Steril Rep 2020.
RESULTS

Baseline characteristics and stimulation outcomes

We enrolled 620 patients in the MEGASET-HR trial, of whom 619 were treated. Three hundred and ten patients were treated with HP-hMG and 309 with recombinant FSH. There were no statistically significant differences in age, body mass index, duration or cause of infertility, or ovarian reserve testing before starting treatment among the patients in each group (6).

Five hundred and ninety-eight patients underwent oocyte retrieval (292 HP-hMG and 306 recombinant FSH), where 530 patients underwent a transfer. Three hundred and ninety-two patients underwent a fresh transfer (201 HP-hMG and 191 recombinant FSH) and 138 patients underwent a first frozen transfer (52 HP-hMG and 86 recombinant FSH). Of all patients who underwent oocyte retrieval in this trial, 68 patients did not undergo a transfer (39 HP-hMG and 29 recombinant FSH). Twenty-one patients did not undergo an oocyte retrieval (18 HP-hMG and 3 recombinant FSH). The costs associated for all treated patients were incorporated in this analysis (Table 2).

Efficacy and safety outcomes

As previously stated, the trial achieved its primary end point of noninferiority in ongoing pregnancy rate per cycle start after fresh transfer of a single blastocyst; this rate was 35.5% in HP-hMG treated patients and 30.7% in those treated with recombinant FSH (6). First-transfer efficacy, defined as live birth after the first transfer (fresh or frozen), was 54.5% (138 of 253) for HP-hMG and 48.0% (133 of 277) for recombinant FSH (difference 6.5%; 95% CI, −2.3% to 15.4%). Corresponding live-birth rates after fresh transfer were 52.2% in patients treated with HP-hMG compared with 48.7% in those treated with recombinant FSH (difference 3.5%; 95% CI, −6.9% to 14.0%), and live-birth rates after first frozen transfer were 63.5% in patients treated with HP-hMG compared with 46.5% in those treated with recombinant FSH (difference 16.9%; 95% CI, −1.4% to 35.3%).

Additionally, HP-hMG treated patients had a lower early pregnancy loss rate in first transfers compared with those treated with recombinant FSH in both fresh transfers (14.3% vs. 23.8%, respectively, for HP-hMG and recombinant FSH; difference: −9.5%; 95% CI: −20.0% to 1.0%) and transfers frozen (12.8% vs. 32.2%, respectively, for HP-hMG and recombinant FSH; difference −19.4%; 95% CI: −37.4% to 1.4%) and well as a lower rate of ovarian hyperstimulation syndrome (9.7% vs. 21.4%, respectively, for HP-hMG and recombinant FSH; difference −11.7%; 95% CI: −17.6% to 5.7%).

Other statistically significant differences between the two treatment groups included total dose and duration of gonadotropin use. The aggregate mean dose for the entire cycle was 2,114.5 ± 798.85 IU in the HP-hMG group compared with 1,498.9 ± 417.36 IU in the recombinant FSH group, a difference of 625.00 IU (95% CI, −450.00 to 600.00). Both treatments were well tolerated with few severe adverse events.

Cost to achieve live birth–first transfer (mITT population)

The average cost per live birth after first transfer (fresh or frozen) in the HP-hMG treatment arm was $32,474 (±$571) compared with $35,784 (±$2,713) in the recombinant FSH treatment arm (Table 3). The difference in treatment cost for patients randomized to the HP-hMG arm compared with those randomized to the recombinant FSH arm was $3,310 (±$2,778; 95% CI, −$5,411 to −$1,209; P < .01).
TABLE 2

First-transfer stimulation results from MEGASET-HR trial.

| Parameter                  | HP-hMG (n = 311) | rFSH (n = 309) |
|----------------------------|------------------|----------------|
| No. of patients treated (mITT) | 310             | 309            |
| Total dose of gonadotropin | 2,114.5 ± 798.65 | 1,498.9 ± 417.36 |
| OHSS, n (%)                | 30 (9.7)         | 66 (21.4)      |
| Mild                       | 7 (2.3)          | 18 (5.8)       |
| Moderate                   | 15 (4.8)         | 39 (12.6)      |
| Severe                     | 8 (2.6)          | 9 (2.9)        |
| No. of patients who completed oocyte retrieval | 292             | 306            |
| No. of patients who completed fresh transfer | 201             | 191            |
| Pregnancy rate, n (%)      | 126 (62.7)       | 122 (63.9)     |
| Early pregnancy loss, n (%)| 18 (14.3)        | 29 (23.8)      |
| Live-birth rate, n (%)     | 105 (52.2)       | 93 (48.7%)     |
| No. of patients who completed frozen transfer | 52              | 86             |
| Pregnancy rate, n (%)      | 39 (75.0)        | 59 (68.6)      |
| Early pregnancy loss, n (%)| 5 (12.8)         | 19 (32.2)      |
| Live-birth rate, n (%)     | 33 (63.5)        | 40 (46.5)      |

Note: First-transfer stimulation results from MEGASET-HR that were used as inputs for the cost minimization model. Classification of OHSS grade was determined using Galan’s classification system. Early pregnancy loss was defined as two positive β-human chorionic gonadotropin tests but no ongoing pregnancy at 10–11 weeks’ gestation. Pregnancy loss after 12 weeks’ gestation was not accounted for in this analysis. HP-hMG = highly purified human menotropin; mITT = modified intent-to-treat; MEGASET-HR = Menopur in Gonadotropin-releasing Hormone Antagonist Single Embryo Transfer–High Responder; OHSS = ovarian hyperstimulation syndrome; rFSH = recombinant follicle stimulating hormone.

a One patient had unknown information on pregnancy loss (earlyfate) that was imputed as early pregnancy loss.

b One patient experienced a pregnancy loss after 12 weeks’ gestation.

c One patient was lost to follow-up after transfer; two patients experienced a pregnancy loss after 12 weeks’ gestation.

d One patient had unknown information on pregnancy loss (earlyfate) that was imputed as early pregnancy loss.

Robins. HP-hMG therapy lowers cost to live birth. Fertil Steril Rep® 2020.

Cost to achieve live birth–fresh transfer

The average cost per live birth after the fresh transfer in the HP-hMG treatment arm was $29,365 (±$485) compared with $31,184 (±$2,437) in the recombinant FSH treatment arm (Table 3). The difference in treatment cost for patients randomized to the HP-hMG arm compared with those randomized to the recombinant FSH arm was $–2,843 (±$2,490; 95% CI, $–4,370, $–597; P < .05).

Cost to achieve live birth–frozen transfer

The average cost per live birth after first frozen transfer in the HP-hMG treatment arm was $26,815 (±$400) compared to $36,360 (±$2,512) in the recombinant FSH treatment arm (Table 3). The difference in treatment cost for patients randomized to the HP-hMG arm compared with those randomized to the recombinant FSH arm was $–9,544 (±$2,548; 95% CI, $–11,483, $–7,605; P < .001).

DISCUSSION

In this cost-minimization analysis from 31 sites in the MEGASET-HR trial, we have shown that the cost to achieve live birth after first transfer was lower for patients treated with HP-hMG compared to those treated with recombinant FSH in both fresh and frozen cycles. The main driver for cost reduction was increased efficiency of live birth after fresh or frozen transfer based upon decreased early pregnancy loss rates in patients treated with HP-hMG. This was most prominent in frozen transfers where early pregnancy loss was statistically significantly lower, and the cost difference in these cases was nearly $10,000 on average.

The MEGASET-HR trial offered a unique opportunity for evaluation of cost per outcome, based upon the type of gonadotropin used in stimulation. All patients were treated in accordance with a standardized protocol that allowed for some flexibility in dosing in the latter part of the cycle. Whereas the diversity in sites and patients recruited based upon geography strengthens the generalizability of the results, dose adjustments permitted after day 6 of treatment reflect typical practice patterns representative of real-world practice. As the protocol prescribed the type and frequency of monitoring and treatment allocation was assessor blind, the paradigms associated with dose adjustments were presumably applied equally to both treatment arms.

The results detailed in this analysis are comparable to other economic analyses performed on data comparing HP-hMG and recombinant FSH. Lloyd et al. [23] demonstrated that HP-hMG is less expensive per treatment cycle and per ongoing pregnancy from a payer perspective compared with recombinant FSH. Connolly et al. [24] derived a model based on published live-birth data from studies comparing HP-hMG to recombinant FSH and success rates using frozen embryos from the Belgian Register for Assisted Procreation (BELRAP) to assess the comparative cost effectiveness of HP-hMG and recombinant FSH. The results of the economic model indicated use of HP-hMG is associated with lower average cost per fresh cycle, lower cumulative cost for one fresh and one cryopreserved cycle, and lower average cost per live birth. Similarly, Wechowski [25] modeled data pooled from two prospective, randomized, multinational trials and found that treatment with HP-hMG after one fresh cycle offers live-birth rates at lower cost compared with recombinant FSH. This trend was maintained even when the scope of the model was expanded to include up to three cycles. Furthermore, when maternal and neonatal costs were incorporated into the analysis, the mean cost per IVF baby delivered was significantly less with HP-hMG compared to recombinant FSH [26]. Barriere et al. [27] used a Markov model to assess the expected cost to live birth using data from two clinical trials and showed a lower cost with HP-hMG. Thus, the results presented in the present study align with those from other economic analyses comparing HP-hMG to recombinant FSH. However, it is the first economic analysis from a patient perspective, conducted in a U.S. population and considering U.S. treatment costs.

In our analysis, itemized costs were obtained from individual sites, and the mean was used as the cost basis. A simple rather than weighted mean was used for calculations so that the results could be generalized to any trial participant rather than be influenced by pricing at a specific center. Otherwise, the differential price reduction would be greater for patients undergoing treatment at more expensive centers and vice versa. Furthermore, the cost of gonadotropin was varied to reflect options available to patients undergoing ART who...
Coverage of ART (3) tends to increase household disposable annual income by just 1%, resulting in a 3.2% increase in fertility coverage by insurers; as a result, most patients continue to personally incur costs associated with fertility care. In states with no mandated insurance coverage, the cost of one fresh IVF cycle amounts to 52% of the average cost of one fresh IVF cycle. In states with no mandate for a variety of reasons, even though frozen embryo transfers predominate nationally (32). The results of this analysis show how protocol choice can favorably impact cost-effectiveness in tandem with efficacy and safety in fresh and frozen transfers to the benefit of patients, providers, and payers.

**TABLE 3**

Average cost to achieve a live birth for first transfer (mITT), fresh transfer, and frozen transfer.

| Procedure                        | HP-hMG  | rFSH  | Difference | Lower bound | Upper bound | P value |
|----------------------------------|---------|-------|------------|-------------|-------------|---------|
| Live birth–first transfer (mITT) | 310     | 309   | -3,310 (2,778) | -5,411      | -1,209      | <.01    |
| Number                           | 32,474 (571) | 35,784 (2,713) |            |             |             |         |
| Cost, $                          | 201     | 191   | -2,483 (2,490) | -4,370      | -597        | <.001   |
| Live birth–frozen transfer       | 52      | 86    | -9,544 (2,548) | -11,483     | -7,605      |         |
| Number                           | 26,815 (400) | 36,360 (2,512) |            |             |             |         |
| Cost                             |         |       |             |             |             |         |

*Note: Cost values are mean ± standard deviation. CI = confidence interval; HP-hMG = highly purified human menotropin; mITT = modified intent-to-treat; rFSH = recombinant follicle stimulating hormone; SD = standard deviation.

Robins. HP-hMG therapy lowers cost to live birth. Fertil Steril Rep 2020.

Improvements in operational efficiency. Promulgation of new insurance mandates in states with no prior coverage, expansion of coverage in states with existing insurance mandates, and an ongoing focus on health economic aspects of overall current medical practice would undoubtedly affect existing treatment paradigms and models. As an example, providers in states with an insurance mandate continue to perform fresh embryo transfers at a higher rate than in states with no mandate for a variety of reasons, even though frozen embryo transfers predominate nationally (32). The results of this analysis show how protocol choice can favorably impact cost-effectiveness in tandem with efficacy and safety in fresh and frozen transfers to the benefit of patients, providers, and payers.

**CONCLUSIONS**

Therapeutic decisions should be based upon an evaluation of safety, efficacy, cost, and treatment experience to optimize patient, provider, and payor interests. This health economic analysis of the recently conducted randomized, controlled MEGASET-HR trial in 619 high responders in the United States provides new insight into how each of these outcomes can be incorporated into a personalized treatment paradigm.

**REFERENCES**

1. Wu AK, Elliott P, Katz PP, Smith JF. Time costs of fertility care: the hidden hardship of building a family. Fertil Steril 2013;99:2025–30.
2. Chambers GM, Adamson GD, Eijkemans MJ. Acceptable cost for the patient and society. Fertil Steril 2013;100:319–27.
3. Chambers GM, Hoang VP, Sullivan EA, Chapman MG, Ishihara O, Zegers-Hochschild F, et al. The impact of consumer affordability on access to assisted reproductive technologies and embryo transfer practices: an international analysis. Fertil Steril 2014;101:191–8.e4.
4. Dyer SJ, Vinoos L, Ataguba JE. Poor recovery of households from out-of-pocket payment for assisted reproductive technology. Hum Reprod 2017;32:2431–6.
5. Gonen LD, Bokek-Cohen Y. Valuing the invaluable: do emotional experiences during fertility treatments affect the willingness to pay for them? Eur Rev Appl Physiol 2018;68:45–60.
6. Witz CA, Daftary GS, Doody KJ, Park JK, Seifu Y, Yankov VI, et al. Randomized, assessor-blinded trial comparing highly purified human menotropin

**Figures and Tables**

- **Figure 1:** Graph illustrating the impact of insurance mandates on the cost of ART.
- **Table 1:** Comparison of median costs for fresh and frozen embryo transfers.
- **Table 2:** Summary of study participants and outcomes.

**Acknowledgments**

The authors acknowledge the contributions of [names of contributors] to the study presented in this article.
and recombinant follicle-stimulating hormone in high responders undergoing intracytoplasmic sperm injection. Fertil Steril 2020;114:F321–30.

7. European and Israeli Study Group on Highly Purified Menotropin versus Recombinant Follicle-Stimulating Hormone. Efficacy and safety of highly purified menotropin versus recombinant follicle-stimulating hormone in in vitro fertilization/intracytoplasmic sperm injection cycles: a randomized, comparative trial. Fertil Steril 2002;78:520–8.

8. Kilani Z, Dakkak A, Ghnaim S, Cognigni G, Tabarelli C, Parmegiani L, et al. A prospective, randomized, controlled trial comparing highly purified hMG with recombinant FSH in women undergoing IVF: a randomized-assessor-blind controlled trial. Hum Reprod 2006;21:3217–27.

9. Andersen AN, Devroey P, Arce JC. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer. Fertil Steril 2012;97:561–71.

10. Devroey P, Pellicer A, Nyboe Andersen A, Arce JC, Group MEGASET. A randomized assessor-blind trial comparing highly purified hMG and recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer. Fertil Steril 2012;97:561–71.

11. Bosch E, Vidal C, Labarta E, Simon C, Remohi J, Pellicer A. Highly purified hMG versus recombinant FSH in ovarian hyperstimulation with GnRH antagonists—a randomized study. Hum Reprod 2008;23:2346–51.

12. Hompes PG, Broekmans FJ, Hoozemans DA, Schats R, Group F. Effectiveness of highly purified human menopausal gonadotropin vs. recombinant follicle-stimulating hormone in first-cycle in vitro fertilization–intracytoplasmic sperm injection patients. Fertil Steril 2008;89:1685–93.

13. Huang J, Huang G, Lei L, Zeng P, Luo X. Outcome of in vitro fertilization following stimulation with highly purified hMG or recombinant FSH in downregulated women of advanced reproductive age: a prospective, randomized and controlled trial. Gynecol Endocrinol 2012;28:540–4.

14. Broer SL, Dolleman M, Opmeer BC, Fauser BC, Mol BW, Broekmans FJ. AMH and AFC as predictors of excessive response in controlled ovarian hyperstimulation: a meta-analysis. Hum Reprod Update 2011;17:46–54.

15. Romero JMS, Ortega Sanchez I, Garcia-Velasco J. The high responder: optimizing the stimulation without complication. In: Arora S, editor. Infertility management series: handbook of ovarian stimulation. London: J.P. Medical; 2018:65–77.

16. Arce JC, Andersen AN, Fernández-Sánchez M, Visnova H, Bosch E, García-Velasco JA, et al. Ovarian response to recombinant human follicle-stimulating hormone: a randomized, anti-mullerian hormone-stratified, dose-response trial in women undergoing in vitro fertilization/intracytoplasmic sperm injection. Fertil Steril 2014;102:1633–40.e5.

17. Arce JC, La Marca A, Mirmer Klein B, Nyboe Andersen A, Fleming R. Anti-mullerian hormone in gonadotropin releasing-hormone antagonist cycles: prediction of ovarian response and cumulative treatment outcome in good-prognosis patients. Fertil Steril 2013;99:1644–53.

18. Chen ZJ, Legro RS. Fresh versus frozen embryos in polycystic ovary syndrome. N Engl J Med 2016;375:e42.

19. Mascarenhas M, Balen AH. The high responder: a review of pathophysiology and outcomes during IVF treatment. Hum Fertil (Camb) 2017;20:155–67.

20. Huseanu D, Drummond M, Petrou S, Carrswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ 2013;346:f1049.

21. Fertility Drug Calculator. Farmers Branch. TX: ViralMD; 2019. Available at: https://www.fertilitydrugcalculator.com/.

22. Rai M, Goyal R. Pharmaco-economics in Healthcare. In: Vohora D, Singh G, editors. Pharmaceutical medicine and translational clinical research. San Diego, CA: Academic Press; 2018:465–72.

23. Lloyd A, Kennedy R, Hutchinson J, Sawyer W. Economic evaluation of highly purified menotropin compared with recombinant follicle-stimulating hormone in assisted reproduction. Fertil Steril 2003;80:1108–13.

24. Connolly M, De Vrieze K, Ombelet W, Schneider D, Currie C. A cost per live birth comparison of rHMG and rFSH randomized trials. Reprod Biomed Online 2008;17:756–63.

25. Wechowski J, Connolly M, Schneider D, McEwan E, Kennedy R. Cost-saving treatment strategies in in vitro fertilization: a combined economic evaluation of two large randomized clinical trials comparing highly purified human menopausal gonadotropin and recombinant follicle-stimulating hormone alpha. Fertil Steril 2009;91:1067–76.

26. Weel-Wechowski J, Abou-Setta A, Nielsen S, Kennedy R. HP-HMG versus rFSH in treatments combining fresh and frozen IVF cycles: success rates and economic evaluation. Reprod BioMed Online 2010;21:166–78.

27. Barriere P, Porcu-Buisson G, Hamamah S. Cost-effectiveness analysis of the gonadotropin treatments HP-hMG and rFSH for assisted reproductive technology in France: a Markov model analysis. Asian Health Econ Policy 2018;16:65–77.

28. Munne S, Kaplan B, Frattarelli JL, Child T, Nakhuda G, Shamma FN, et al. Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial. Fertil Steril 2019;112:1071–9.e7.

29. Murugappan G, Ohno MS, Lathi RB. Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss. Fertil Steril 2015;103:1215–20.

30. Neal SA, Morin SJ, Fransasiak JM, Goodman LR, Juneau CR, Forman EJ, et al. Preimplantation genetic testing for aneuploidy is cost-effective, shortens treatment time, and reduces the risk of failed embryo transfer and clinical miscarriage. Fertil Steril 2018;110:896–904.

31. Huang L, Bogale B, Tang Y, Lu S, Xie XS, Racowsky C. Noninvasive preimplantation genetic testing for aneuploidy in spent medium may be more reliable than trophectoderm biopsy. Proc Natl Acad Sci USA 2019;116:14105–12.

32. Boulet SL, Crawford S, Zhang Y, Sunderland S, Cohen B, Bernson D, et al. Embryo transfer practices and perinatal outcomes by insurance mandate status. Fertil Steril 2015;104:403–9.e1.

33. Csokmay JM, Yaujer BJ, Henne MB, Armstrong AY, Queenan JT, Segars JH. Cost analysis model of outpatient management of ovarian hyperstimulation syndrome with paracetamol: “tap early and often” versus hospitalization. Fertil Steril 2010;93:167–73.