Survey Report

Perception mapping of Indian Physicians on Corifollitropin alfa (CFA) in controlled ovarian stimulation (COS)

Version No.: 1.1

The study was conducted according to the approved protocol and in compliance with the protocol, Good Clinical Practice (GCP), and other applicable local regulatory requirements.

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1 INTRODUCTION

Infertility affects 10-15% of couples attempting to conceive [1, 2]. Assisted reproductive technologies (ART) offer the best likelihood of success for these couples. Although the first ART pregnancy occurred during a natural cycle, it was quickly discovered that the amount of oocytes available for in vitro fertilization (IVF) increased the chances of success [3]. The development of gonadotropin-releasing hormone (GnRH) agonists (GnRHa) allowed for the suppression of early luteinizing hormone (LH) surges in stimulated cycles, as well as the scheduling of oocyte retrieval. Thus, controlled ovarian hyperstimulation (COS) and its two components, gonadotropin and GnRHa, became an essential component of the ART cycle [4]. COS has been shown to boost the success rate of IVF, with most treatment centers achieving outcomes that exceed spontaneous conception rates in healthy viable couples [5].

The development which further simplifies ART treatment is the introduction of corifollitropin alfa, a long-acting recombinant follicle-stimulating hormone (rFSH) molecule. A single injection of corifollitropin alfa (CFA) can replace daily gonadotropin injections for 7 days and can further decrease the number of injections required in a COS cycle [6-10]. The relatively short t½ of the wild-type FSH molecule (WT-FSH) requires once daily dosing for COS. Corifollitropin alfa was shown to be ten times more biopotent than WT-FSH. One study found that a single injection of 10 IU CFA was sufficient to accelerate follicular maturation in rats, allowing hCG to trigger ovulation 52 hours later. In contrast, a single injection of 10 IU WT-FSH had no effect on boosting ovulatory potential, whereas the same total dose of WT-FSH, provided as four consecutive 2.5 IU injections 12 hours apart, was as efficacious as CFA [11].

Overall, while CFA in controlled ovarian stimulation (COS) is a useful rFSH for specific conditions like COS, its use in vulnerable populations such as infertile women, and ART. Continuous monitoring and further studies are necessary to better understand its safety and efficacy across these groups.

2 RATIONALE OF THE STUDY

The rationale for mapping the perception of Indian physicians regarding Corifollitropin alfa (CFA) in controlled ovarian stimulation (COS) is rooted in the evolving landscape of fertility treatment and the need to understand how advanced therapeutic options are received in different cultural and clinical contexts. CFA is a novel gonadotropin used in COS, simplifying the IVF process by reducing the frequency of daily injections needed during the initial stimulation phase. Given the stress and complexity associated with conventional IVF protocols, CFA presents a significant advancement in patient compliance and comfort. Mapping physician perceptions will reveal the acceptance and perceived benefits of CFA among practitioners, as well as their concerns, which could guide further education and potential adjustments in practice guidelines for optimized use.

Additionally, understanding physicians' views is crucial because it reflects broader implications for patient outcomes and satisfaction. Indian physicians operate in a unique healthcare environment with varied patient demographics, financial constraints, and cultural sensitivities around infertility. Investigating how CFA is viewed could shed light on the challenges faced when implementing new fertility treatments and highlight opportunities for improving patient care. Insights gained from this mapping exercise can inform pharmaceutical strategies, assist in customizing patient education, and ultimately contribute to advancing reproductive health services in India.

3 STUDY OBJECTIVE

To assess the perception, practice patterns, and clinical experiences of Indian physicians regarding the Corifollitropin alfa (CFA) in controlled ovarian stimulation (COS).

4 METHODS

This study will employ a cross-sectional, questionnaire-based survey methodology to explore the perceptions, practices, and clinical experiences of Indian physicians regarding the use of CFA (corticosteroid-free alternatives) in the management of COS (chronic orthopedic syndromes). a structured, 14-item electronic questionnaire will be distributed to a diverse and representative sample of licensed physicians across india. Participants will be identified through professional networks and

medical associations and will include general practitioners and specialists who have treated COS cases within the last year. The inclusion criteria ensure participants have relevant clinical experience, while exclusion criteria exclude medical students, administrative staff, and physicians not actively involved in patient care.

Upon consent, participants will complete the questionnaire electronically, with responses collected and stored securely. The survey is designed to gather data on treatment frequency, safety and efficacy perceptions of CFA, and the factors influencing its therapeutic indication. Descriptive statistics will summarize participant demographics and overall response trends, providing a snapshot of current practices. Inferential statistical methods, such as chi-square tests or logistic regression, may be employed to identify associations between physician characteristics (e.g., specialty, region) and their perceptions or prescribing behaviors.

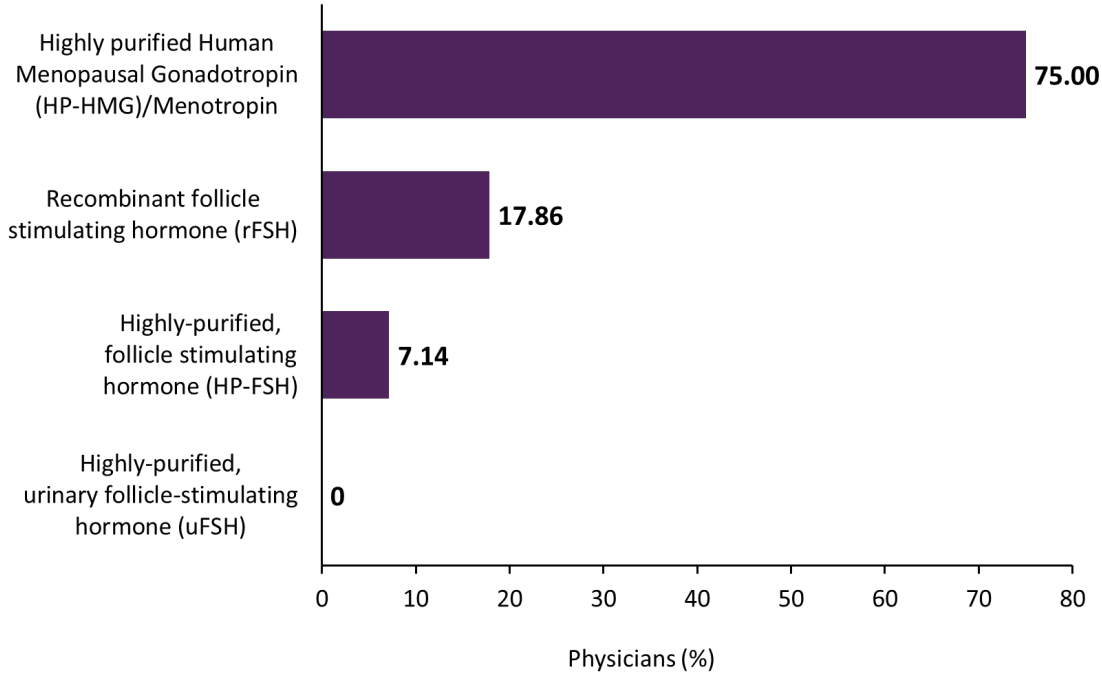
Ethical considerations include obtaining approval from an Independent Ethics Committee and adhering to the Declaration of Helsinki. Participant confidentiality will be maintained by anonymizing responses, and individuals will retain the right to withdraw at any stage without consequence. The findings will be compiled into a report and shared through scientific publications or presentations to inform clinical guidelines and future research. This methodology ensures robust data collection while respecting ethical standards and capturing a comprehensive understanding of CFA use in COS management.

5 RESULTS

A total of 84 HCPs participated in the survey. Below is the summary of the responses.

1. Which of the following gonadotropins is your treatment of choice in controlled ovarian stimulation (COS)?

A. Highly purified Human Menopausal Gonadotropin (HP-HMG)/Menotropin
B. Recombinant follicle stimulating hormone (rFSH)
C. Highly-purified, follicle stimulating hormone (HP-FSH)
D. Highly-purified, urinary follicle-stimulating hormone (uFSH)

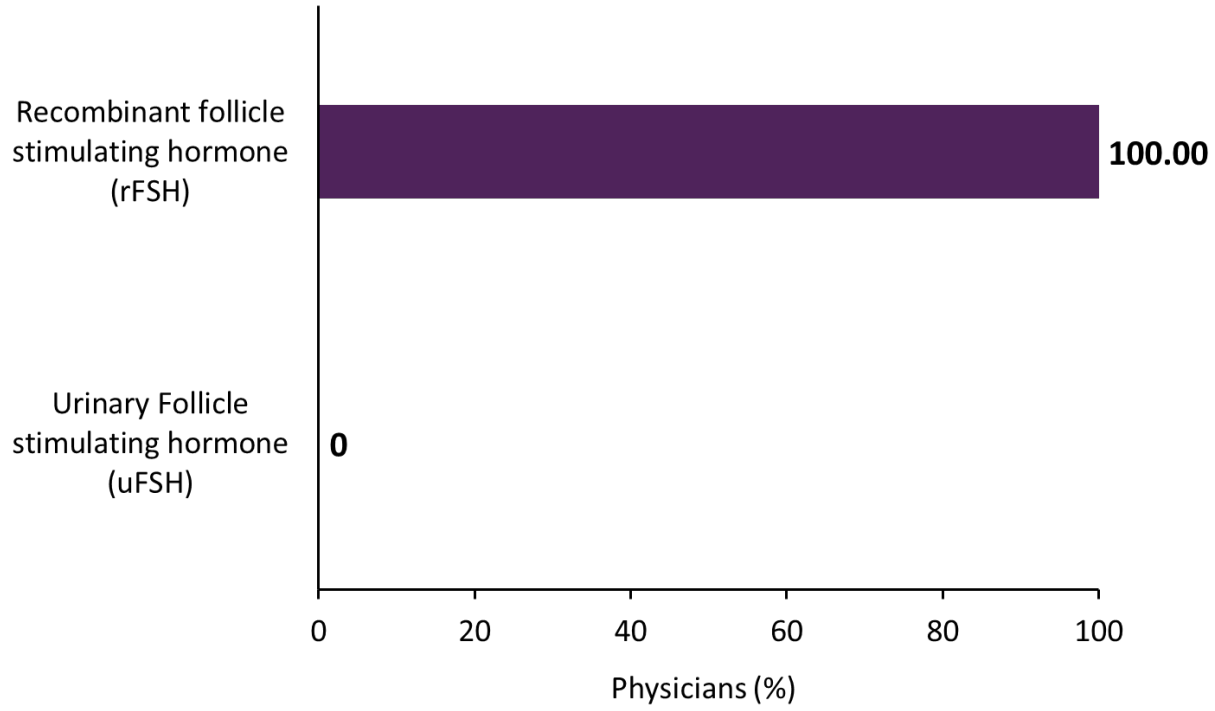


- The majority (75.00%) of physicians use highly purified human menopausal gonadotropin (HP-HMG)/menotropin as the treatment of choice in controlled ovarian stimulation (COS).
- Around 17.86% of physicians use recombinant follicle stimulating hormone (rFSH) as the treatment of choice in controlled ovarian stimulation (COS).
- Approximately 7.14% of physicians use highly-purified, follicle stimulating hormone (HP-FSH) as the treatment of choice in controlled ovarian stimulation (COS).
- No physicians opted for Highly-purified, urinary follicle-stimulating hormone (uFSH) as the treatment of choice in controlled ovarian stimulation (COS).

2. Which of the follicle stimulating hormone (FSH) formulation do you prefer the most in your practice?

A. Urinary Follicle stimulating hormone (uFSH)

B. Recombinant Follicle stimulating hormone (rFSH)



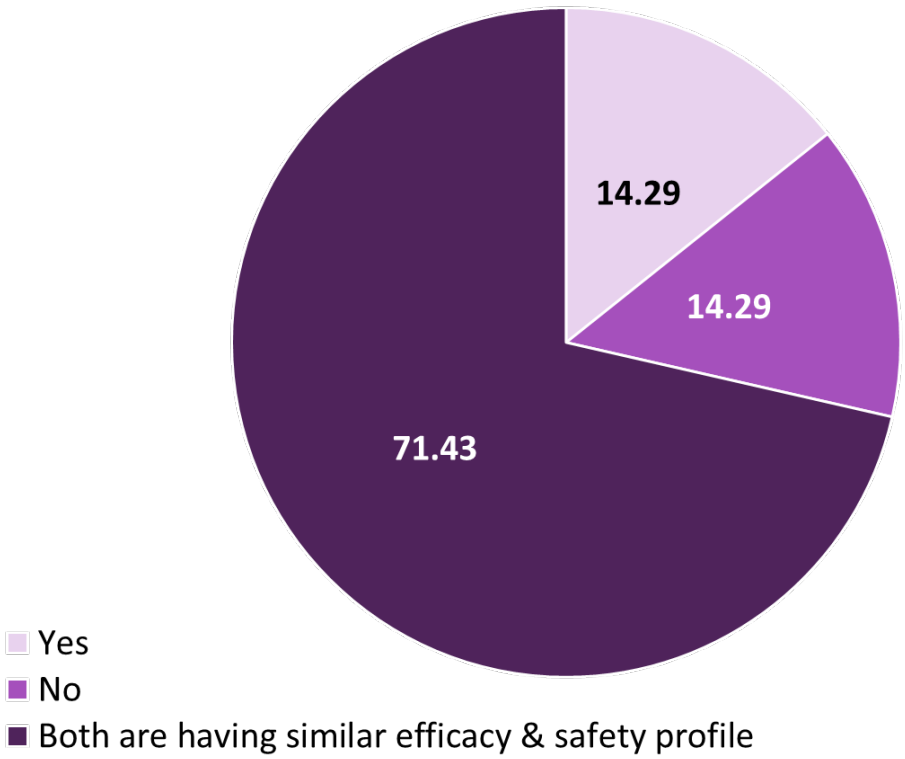
- All of the physicians (100.00%) in the survey preferred recombinant follicle stimulating hormone (rFSH) in their practice and no physicians opted for urinary stimulating hormone (uFSH)

3. Do you consider rFSH superior to HMG?

A. Yes

B. No

C. Both are having similar efficacy & safety profile



- According to majority (71.43%) of physicians both rFSH and HMG both have similar efficacy and safety profile.
- Equal portion (14.29%) of two sets of physicians agree as well as do not agree that rFSH superior to HMG.

4. In what % of your infertility patients do you prefer rFSH over HMG?

A. 1-10%

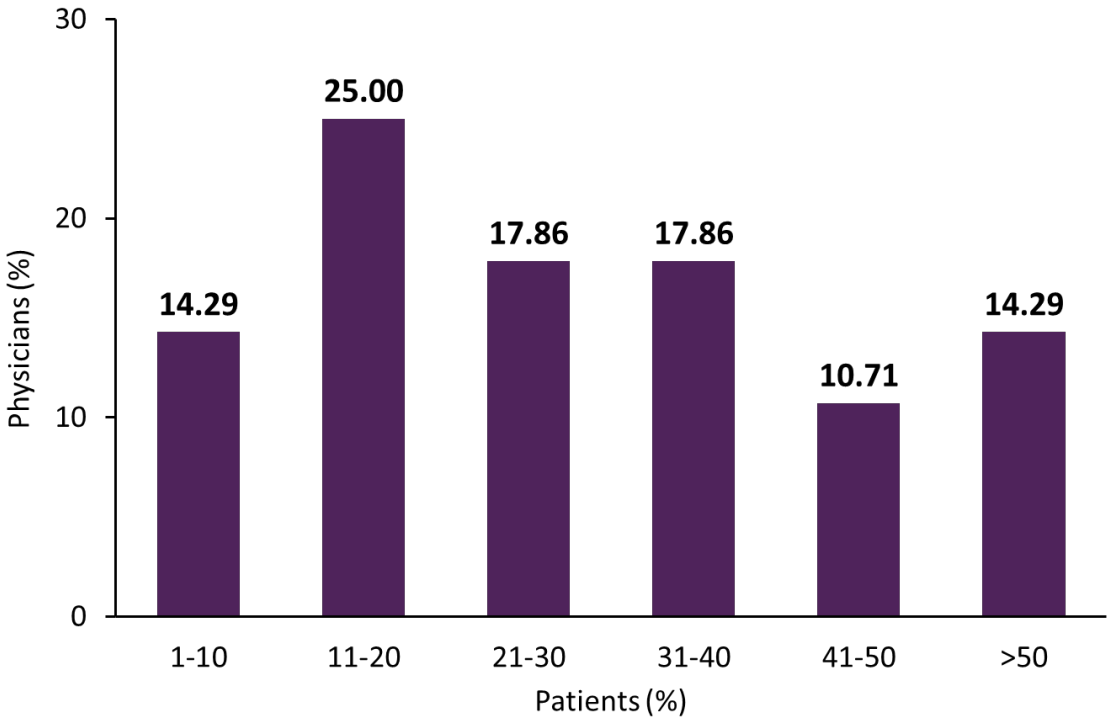
B. 11-20%

C. 21-30%

D. 31-40%

E. 41-50%

F. >50%



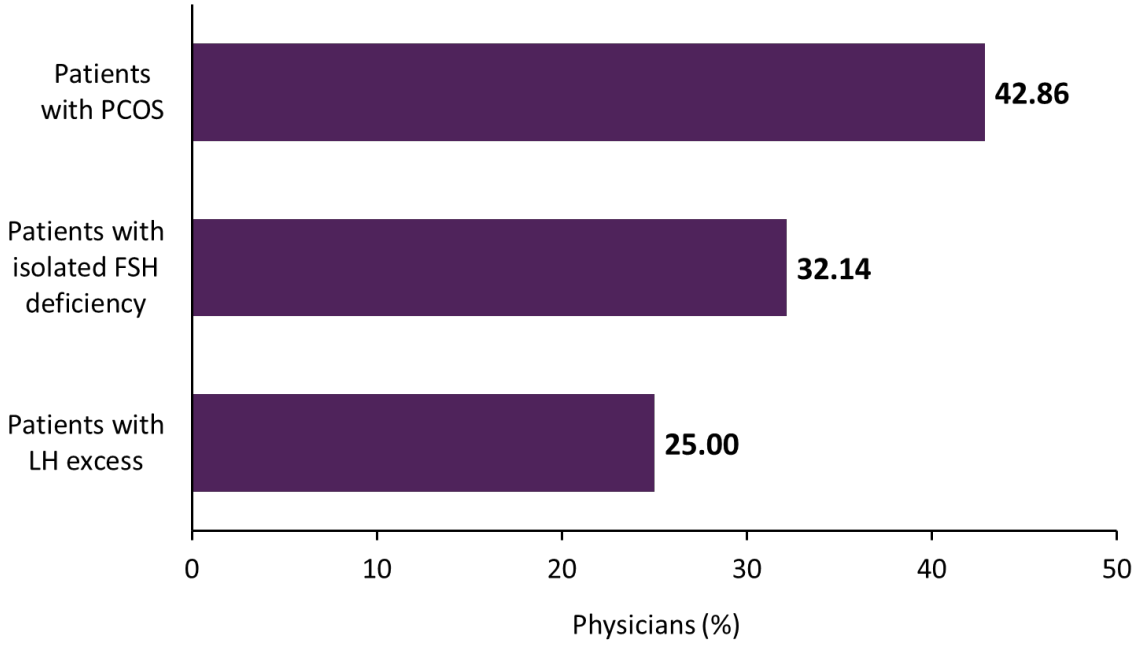
- Around 25.00% of physicians prefer rFSH over HMG in 11-20% of their infertility patients.
- About 10.71% of physicians prefer rFSH over HMG in 41-50% of their infertility patients.
- Similarly two sets of (17.86%) of physicians prefer rFSH over HMG in 21-30% and 31-40% of their infertility patients.
- A significant portion (14.29%) of two sets of physicians prefer rFSH over HMG in 1-10% and more than 50% of their infertility patients.

5. In which of the following patient profiles do you prefer rFSH over other gonadotropins? (you can click more than 1 option)

A. Patients with LH excess

B. Patients with PCOS

C. Patients with isolated FSH deficiency



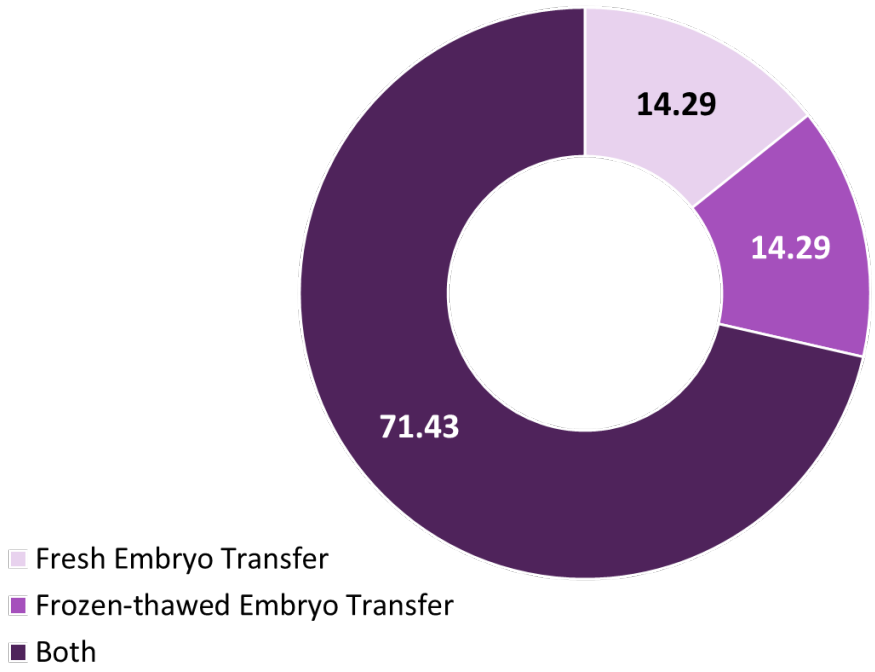
- Around 42.86% of physicians prefer rFSH over other gonadotropins in patients with PCOS.
- Approximately, 32.14% of physicians prefer rFSH over other gonadotropins in patients with isolated FSH deficiency.
- A notable portion (25.00%) of physicians prefer rFSH over other gonadotropins in patients with LH excess.

6. In which of the following cases do you prefer using rFSH?

A. Fresh Embryo Transfer

B. Frozen-thawed Embryo Transfer

C. Both

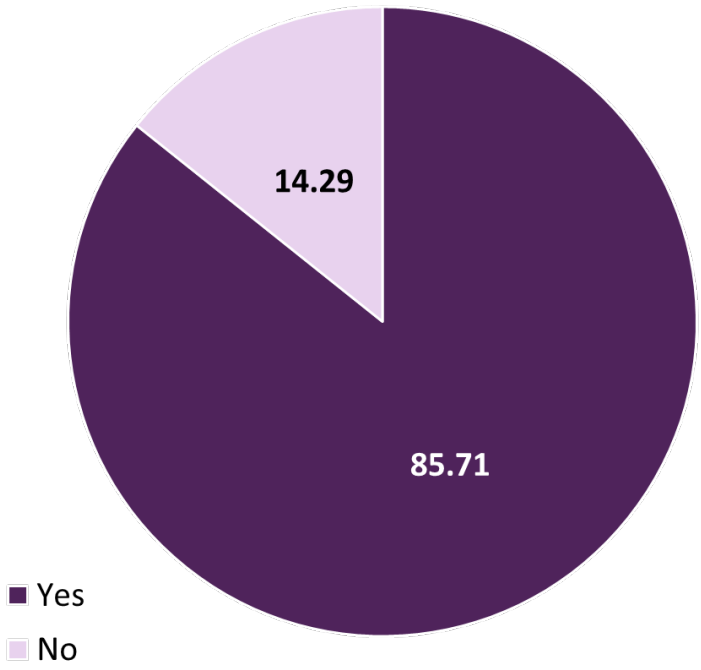


- A majority (71.43%) of physicians prefer rFSH in fresh embryo transfer as well as frozen-thawed embryo transfer
- Around two sets 14.29% of physicians prefer rFSH in fresh embryo transfer and frozen-thawed embryo transfer

7. Do you use HP-HMG in combination with recombinant follicle stimulating hormone (rFSH) in your patients with infertility?

A. Yes

B. No

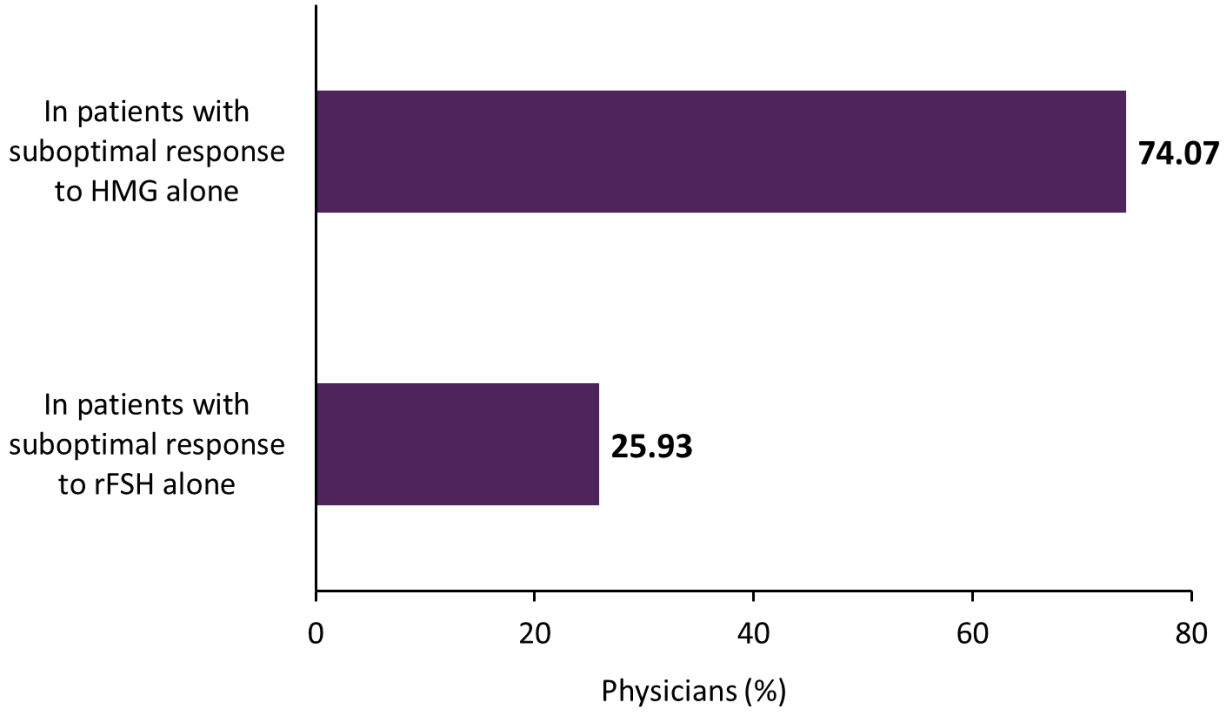


- A majority (85.71%) of physicians use HP-HMG in combination with recombinant follicle stimulating hormone (rFSH) in their patients with infertility.
- Contrastly, 14.29% of physicians do not use HP-HMG in combination with recombinant follicle stimulating hormone (rFSH) in their patients with infertility.

8. In which of the following conditions or patient profiles, do you prefer using HP-HMG plus rFSH?

A. In patients with suboptimal response to rFSH alone

B. In patients with suboptimal response to HMG alone



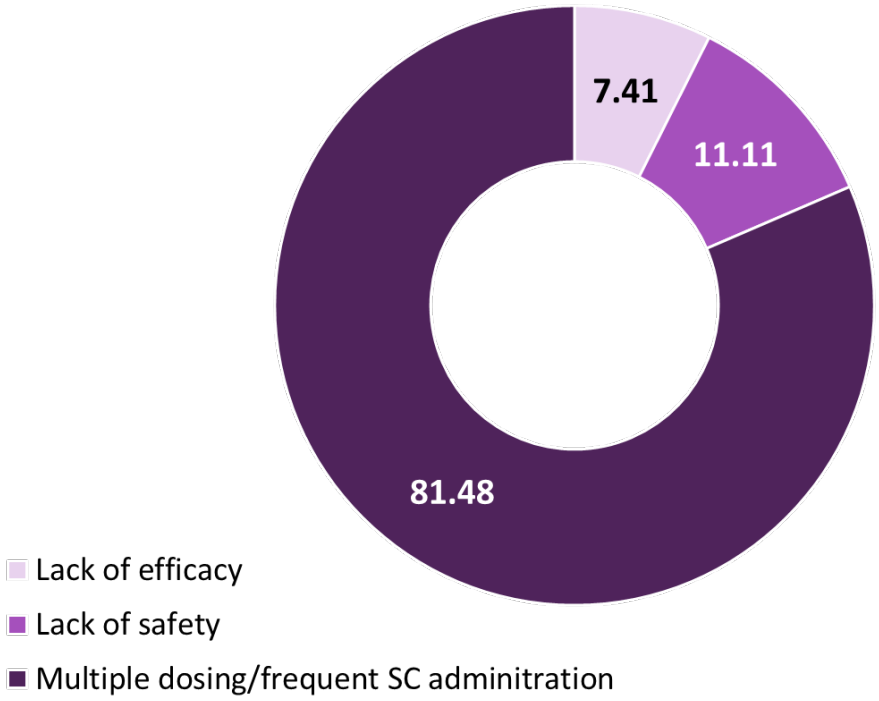
- The majority (74.07%) of physicians prefer using HP-HMG plus rFSH In patients with suboptimal response to rFSH alone.
- Around 25.93% of physicians prefer using HP-HMG plus rFSH in patients with suboptimal response to HMG alone.

9. What according you are the main challenges with HMG/rFSH in COS?

A. Lack of efficacy

B. Lack of safety

C. Multiple dosing/frequent SC administration



- According to the majority (81.48%) of physicians, the main challenge with HMG/rFSH in COS is multiple dosing/frequent SC administration.
- Around 11.11% of physicians observed lack of safety as the main challenge with HMG/rFSH in COS is multiple dosing/frequent SC administration.
- A small portion (7.41%) of physicians noted lack of efficacy as the main challenge with HMG/rFSH in COS is multiple dosing/frequent SC administration.

10. In your clinical practice, what is the discontinuation rate with rFSH due to frequent SC administration?

A. 1-10%

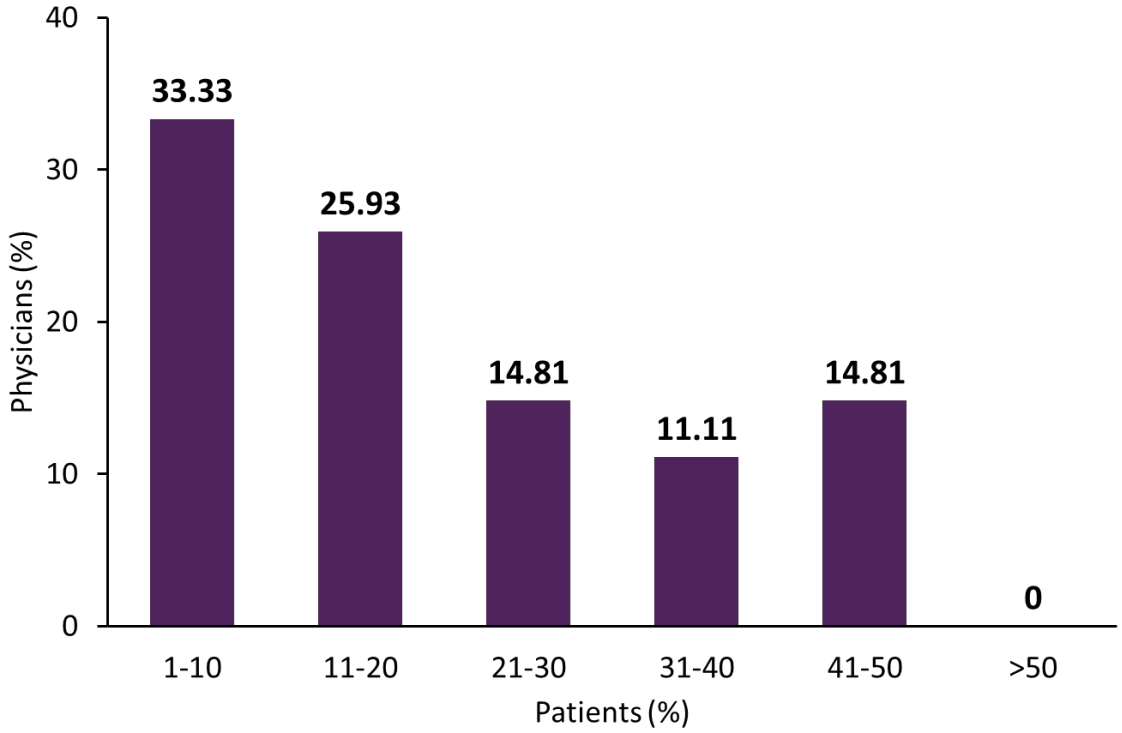
B. 11-20%

C. 21-30%

D. 31-40%

E. 41-50%

F. >50%



- Around (33.33%) of physicians observed 1-10% of patients discontinuing rFSH due to frequent SC administration.
- A notable portion (25.93%) of physicians noted 11-20% of patients discontinuing rFSH due to frequent SC administration.
- About two sets (14.81%) of physicians reported 21-30% and 41-50% of patients discontinuing rFSH due to frequent SC administration.
- Approximately, 11.11% of physicians estimated 31-40% of patients discontinuing rFSH due to frequent SC administration.
- No physicians observed more than 50% of patients discontinuing rFSH due to frequent SC administration.

11. How commonly do you encounter side effects mainly Ovarian Hyper Stimulation Syndrome (OHSS) with rFSH?

A. 1-10%

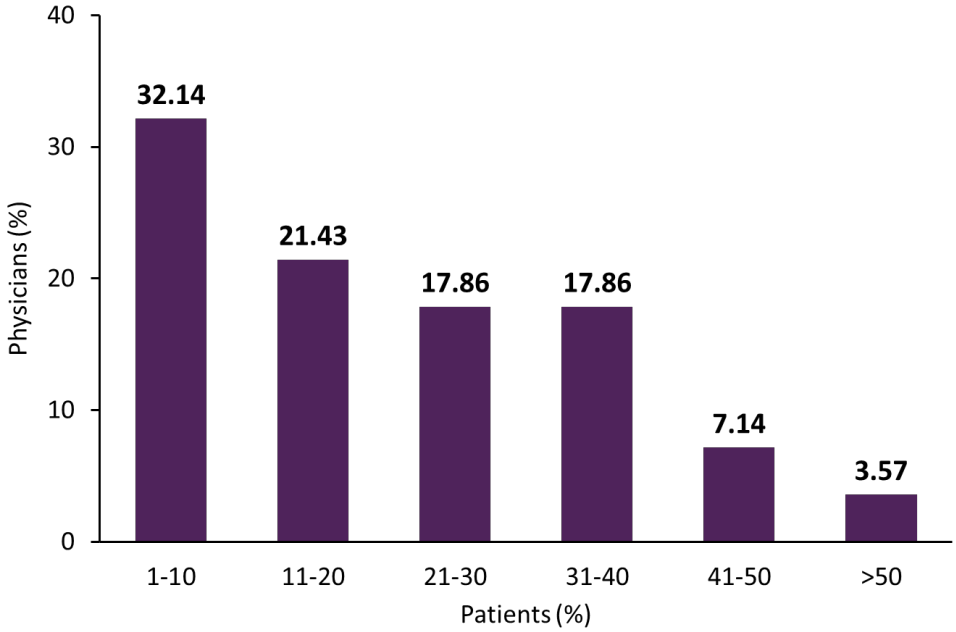
B. 11-20%

C. 21-30%

D. 31-40%

E. 41-50%

F. >50%



- Around 32.14% of physicians observed 1-10% of patients encounter side effects mainly Ovarian Hyper Stimulation Syndrome (OHSS) with rFSH.
- About 21.43% of physicians noted 11-20% of patients encounter side effects mainly Ovarian Hyper Stimulation Syndrome (OHSS) with rFSH.
- Approximately, 17.86% of two sets of physicians reported 21-30% and 31-40% of patients encounter side effects mainly Ovarian Hyper Stimulation Syndrome (OHSS) with rFSH.
- A notable portion (7.14%) of physicians estimated 41-50% of patients encounter side effects mainly Ovarian Hyper Stimulation Syndrome (OHSS) with rFSH.
- A small portion (3.57%) of phhysicians reported more than 50% of patients encounter side effects mainly Ovarian Hyper Stimulation Syndrome (OHSS) with rFSH.

12. What according to you should be the properties of an ideal gonadotropin/rFSH preparation? (you can select more than one options)

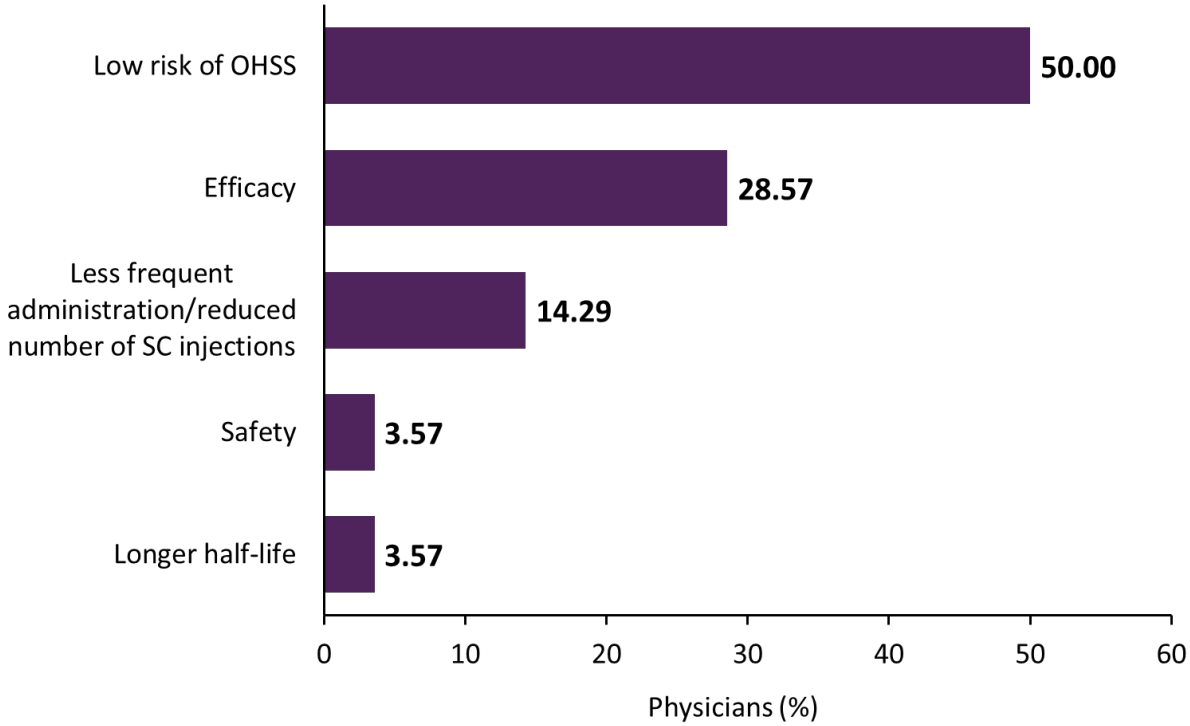
A. Efficacy

B. Safety

C. Longer half-life

D. Less frequent administration/reduced number of SC injections

E. Low risk of OHSS

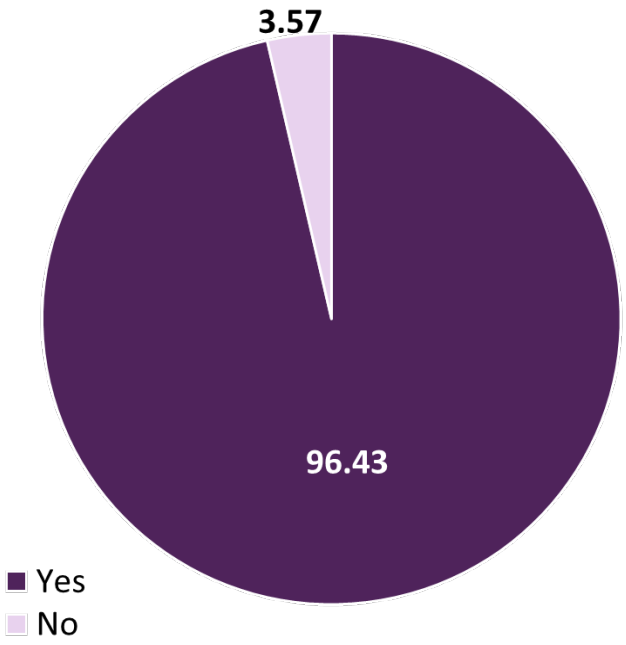


- The majority (50.00%) of physicians observed low risk of OHSS as an ideal property of gonadotropin/rFSH preparation.
- Around 28.57% of physicians noted efficacy as an ideal property of gonadotropin/rFSH preparation.
- About 14.29% of physicians estimated less frequent administration/reduced number of SC injections as an ideal property of gonadotropin/rFSH preparation.
- Approximately, two sets of 3.57% of physicians reported safety and longer-half life as an ideal property of gonadotropin/rFSH preparation.

13. Corifollitropin alfa (CFA) is a long-acting recombinant follicle stimulating hormone (rFSH) with well-established safety & efficacy in clinical trials. A single injection of CFA can initiate and sustain the multiple follicular growth for the first seven days of COS, due to a slower absorption and a much longer elimination half time (68 Hrs). Do you think such formulation will be beneficial and improve adherence of patients due to reduced number of SC injections?

A. Yes

B. No



- The majority (96.43%) of physicians believes such formulation will be beneficial and improve adherence of patients due to reduced number of SC injections.
- A small portion (3.57%) of physicians do not believe such formulation will be beneficial and improve adherence of patients due to reduced number of SC injections.

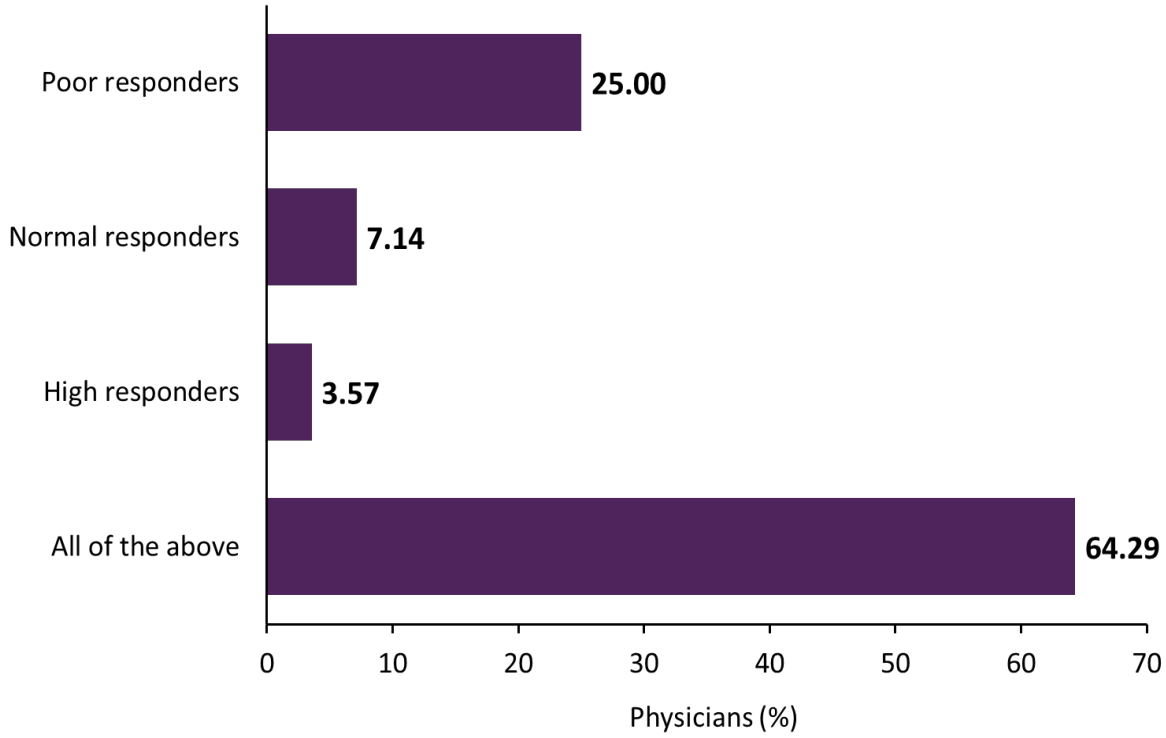
14. Which of the following patient profiles would be suitable candidates for long acting Corifollitropin alfa (CFA)?

A. Poor responders

B. Normal responders

C. High responders

D. All of the above



- Around 25.00% of physicians believe poor responders would be the suitable candidate for long acting Corifollitropin alfa (CFA).
- Approximately 7.14% of physicians observed normal responders as the suitable candidate for long acting Corifollitropin alfa (CFA).
- About 3.57% of physicians noted high responders as the suitable candidate for long acting Corifollitropin alfa (CFA).
- The majority (64.29%) of physicians reported all of the above as the the suitable candidate for long acting Corifollitropin alfa (CFA).

6 SUMMARY

The majority of physicians (75%) prefer highly purified human menopausal gonadotropin (HP-HMG)/menotropin for controlled ovarian stimulation (COS), followed by 17.86% favoring recombinant follicle-stimulating hormone (rFSH), while 7.14% use highly purified FSH (HP-FSH). None opted for highly purified urinary FSH (uFSH). Most physicians (71.43%) find rFSH and HMG equally effective and safe, though opinions vary on whether rFSH is superior. A significant portion (85.71%) use HP-HMG with rFSH for infertility, particularly when patients respond suboptimally to either agent alone. Challenges in using these agents include frequent subcutaneous (SC) injections (81.48%) and patient discontinuation due to this factor, observed in 1-50% of cases.

Side effects, particularly ovarian hyperstimulation syndrome (OHSS), are noted, with 32.14% observing it in 1-10% of patients and smaller proportions reporting higher rates. Ideal properties of gonadotropin/rFSH preparations include low OHSS risk (50%), efficacy (28.57%), and reduced SC injections (14.29%). Most physicians (96.43%) believe such improvements would enhance adherence. In special cases, rFSH is preferred for patients with polycystic ovary syndrome (42.86%), isolated FSH deficiency (32.14%), and LH excess (25%). It is also favored in both fresh and frozen-thawed embryo transfers (71.43%). Long-acting corifollitropin alfa (CFA) is considered suitable for poor responders (25%), normal responders (7.14%), and high responders (3.57%), with the majority (64.29%) endorsing its use for all groups. Overall, a combination of HP-HMG and rFSH remains a favored strategy to address COS complexities while managing patient-specific needs.

7 DISCUSSION

Controlled ovarian stimulation (COS) is a cornerstone of assisted reproductive technology, and selecting the appropriate gonadotropin plays a crucial role in treatment outcomes. The majority (75%) of physicians prefer using highly purified human menopausal gonadotropin (HP-HMG) or menotropin for COS due to its proven efficacy in stimulating ovarian follicles. Around 17.86% of physicians favor recombinant follicle-stimulating hormone (rFSH), while only 7.14% opt for highly purified FSH (HP-FSH). None of the surveyed physicians recommended urinary follicle-stimulating hormone (uFSH) for COS, indicating a shift towards more advanced and effective formulations. Physicians generally agree on the efficacy and safety profiles of rFSH and HP-HMG, with 71.43% stating that both are comparable. Opinions on whether rFSH is superior to HP-HMG are split, with 14.29% each agreeing and disagreeing, reflecting variability in clinical experiences and patient-specific outcomes. Many physicians (85.71%) use a combination of HP-HMG and rFSH to maximize stimulation, particularly in suboptimal responders. Specifically, 74.07% prefer this combination when rFSH alone proves insufficient, while 25.93% use it when HP-HMG alone underperforms.

The choice of gonadotropin also depends on patient characteristics. For instance, 42.86% prefer rFSH for patients with polycystic ovary syndrome (PCOS), 32.14% for those with isolated FSH deficiency, and 25% for patients with luteinizing hormone (LH) excess. Additionally, rFSH is preferred by 71.43% of physicians for both fresh and frozen-thawed embryo transfers, underscoring its versatility in different IVF protocols.Challenges with gonadotropins, particularly multiple subcutaneous (SC) administrations, were noted by 81.48% of physicians as a significant issue affecting patient compliance. Frequent dosing led to rFSH discontinuation in up to 41-50% of cases, depending on the physician's practice, with 33.33% observing a low discontinuation rate of 1-10%. Adverse effects such as ovarian hyperstimulation syndrome (OHSS) were reported in varying frequencies, with 32.14% observing side effects in 1-10% of patients, highlighting the importance of low OHSS risk as an ideal gonadotropin characteristic. Physicians also value efficacy (28.57%), reduced SC injections (14.29%), safety, and longer half-life, though the latter two were noted by smaller proportions.

Regarding emerging treatments, 96.43% of physicians believe long-acting formulations, such as corifollitropin alfa (CFA), could enhance adherence by reducing injection frequency. CFA is seen as particularly suitable for poor responders (25%) and normal or high responders by smaller groups. Overall, 64.29% consider it effective across diverse patient profiles, suggesting a potential paradigm shift in COS management. In summary, while HP-HMG remains the preferred gonadotropin for COS, rFSH's popularity reflects its adaptability and safety profile. Combining these agents is common in managing suboptimal responders. Despite challenges like frequent SC injections, advances in gonadotropin formulations and the introduction of long-acting agents like CFA offer promising solutions to enhance patient adherence and outcomes. Physicians' preferences indicate a balance between efficacy, safety, and patient-centered approaches in selecting gonadotropins for infertility treatment.

8 CLINICAL RECOMMENDATIONS

- Controlled ovarian stimulation (COS) is a cornerstone in infertility treatment, and the choice of gonadotropins plays a significant role in optimizing outcomes.
- Based on physician preferences and clinical observations, highly purified human menopausal gonadotropin (HP-HMG) is the most commonly used agent, preferred by 75% of physicians, followed by recombinant follicle-stimulating hormone (rFSH) and highly purified FSH (HP-FSH).
- Physicians overwhelmingly support rFSH (100%) in practice, highlighting its perceived efficacy and safety profile.
- Moreover, 71.43% of physicians agree that rFSH and HMG exhibit similar efficacy and safety, although some prefer rFSH for specific patient groups, such as those with polycystic ovary syndrome (42.86%), isolated FSH deficiency (32.14%), and luteinizing hormone (LH) excess (25%).
- Combination protocols, such as HP-HMG with rFSH, are widely adopted (85.71%) to address suboptimal responses to single-agent therapy. However, challenges like frequent subcutaneous (SC) administration and associated patient non-adherence remain significant, with up to 50% of physicians observing discontinuation rates tied to these factors.
- Side effects, notably ovarian hyperstimulation syndrome (OHSS), were reported in varying degrees, with most physicians associating a lower risk of OHSS with the ideal gonadotropin preparation.
- A majority (96.43%) emphasized the importance of reduced SC injections for improving adherence, and there is strong support for long-acting formulations like corifollitropin alfa (CFA), with 64.29% of physicians identifying it as suitable for a broad range of patients, including poor, normal, and high responders.
- To optimize COS outcomes, clinicians should prioritize individualizing gonadotropin selection based on patient-specific characteristics and treatment goals.
- Leveraging combination protocols, long-acting formulations, and preparations with reduced injection frequency may enhance adherence, minimize risks, and improve overall treatment success.

9 CONSULTANT OPINION

The survey findings highlight diverse physician preferences and practices in controlled ovarian stimulation (COS), reflecting a nuanced approach to infertility treatment. A significant majority (75%) of physicians favor highly purified human menopausal gonadotropin (HP-HMG)/menotropin, underscoring its established efficacy and safety profile. However, recombinant follicle-stimulating hormone (rFSH) also holds importance, with all physicians incorporating it into their practice, primarily for its perceived advantages in specific patient subgroups. Notably, no physician opted for urinary gonadotropins, indicating a clear preference for purified and recombinant preparations.While most physicians (71.43%) consider rFSH and HMG equally effective and safe, a minority (14.29%) disagrees, suggesting variability in clinical outcomes or patient-specific considerations. In practice, rFSH is often preferred for patients with polycystic ovarian syndrome (PCOS) (42.86%), isolated FSH deficiency (32.14%), or luteinizing hormone (LH) excess (25%). The combination of HP-HMG and rFSH is favored by 85.71% of physicians, particularly in patients with suboptimal responses to rFSH alone (74.07%).

Challenges such as frequent subcutaneous (SC) administration and associated discontinuation rates were commonly reported. Over one-third (33.33%) of physicians observed 1–10% of patients discontinuing treatment due to frequent injections, emphasizing the need for formulations with reduced administration frequency. Side effects, predominantly ovarian hyperstimulation syndrome (OHSS), remain a concern, with varying incidence rates observed across patient subsets. Physicians expressed a preference for gonadotropin formulations with low OHSS risk (50%), high efficacy (28.57%), and less frequent administration (14.29%). Most (96.43%) believe such innovations could enhance adherence. Long-acting corifollitropin alfa (CFA) is seen as suitable for various responder profiles, particularly poor responders (25%) and all categories (64.29%), highlighting its versatility in COS protocols. Overall, these findings underscore the importance of tailoring treatment to patient needs while addressing administration challenges to improve outcomes and adherence.

10 MARKET OPPORTUNITIES

The field of COS presents significant opportunities for innovation and growth, driven by the increasing demand for more effective and patient-friendly infertility treatments. The overwhelming reliance on HP-HMG and rFSH underscores the need for products that balance efficacy and convenience. A key area of opportunity lies in developing long-acting gonadotropins, such as corifollitropin alfa (CFA), which could address the primary challenges of frequent SC administration and improve patient adherence. With 96.43% of physicians supporting such innovations, there is a clear demand for formulations that reduce the burden of daily injections.

Additionally, addressing the side effect profile of rFSH, especially OHSS, could create a competitive edge in the market. By focusing on lower OHSS risk and improved safety profiles, manufacturers could cater to the 50% of physicians prioritizing these properties in gonadotropin preparation. Furthermore, expanding the indications of rFSH and CFA to cover a broader spectrum of infertility patients, including those with PCOS, LH excess, and FSH deficiency, can capture a wider patient base. Physicians' preferences for combination therapies, particularly HP-HMG and rFSH, present another opportunity to develop optimized multi-action formulations. The high rate of suboptimal responders to current therapies also highlights the need for personalized treatment protocols and advanced products tailored to specific patient profiles. By addressing these unmet needs, pharmaceutical companies can establish themselves as leaders in the infertility treatment market.

11 MARKET POSITIONING

- Long-acting Corifollitropin alfa (CFA) is well-positioned to address key challenges in COS treatment. With frequent SC injections cited as a significant barrier by 81.48% of physicians and discontinuation rates reaching up to 50%, CFA offers a much-needed solution.
- By reducing the injection burden, CFA not only enhances adherence but also addresses patient discomfort and logistical concerns, a critical factor supported by 96.43% of surveyed physicians.
- Additionally, its efficacy across patient types—poor, normal, and high responders—appeals to a broad spectrum of clinical scenarios, with 64.29% of physicians viewing it as suitable for all categories.
- CFA's potential to lower the risk of ovarian hyperstimulation syndrome (OHSS), coupled with its ability to maintain efficacy, aligns with physicians' priorities for ideal gonadotropin preparations.
- With 50.00% of physicians emphasizing low OHSS risk as an essential feature and 28.57% prioritizing efficacy, CFA strikes a balance between safety and performance.
- Moreover, the reduced dosing frequency caters to a growing demand for convenience, highlighted by 14.29% of physicians who prioritize reduced injection frequency as a critical improvement.
- CFA's unique positioning as a long-acting, effective, and patient-centric solution makes it a compelling choice in the COS market.
- By addressing unmet needs, including adherence and safety, CFA has the potential to become a first-line option in infertility treatments.
- Its appeal to both physicians and patients ensures a strong foothold in the competitive landscape of gonadotropins.

12 REFERENCES

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