Survey Report

Human Chorionic Gonadotropin and Human Menopausal Gonadotropin Protocol in IVF

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 is considered a major public health issue, as it affects about 15% of reproductively- aged couples. [1] The International Committee defines infertility for Monitoring Assisted Reproductive Technology (ICMART) and WHO as the 'failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse'. [2] Approximately 85% of infertile couples have an identifiable cause. The most common causes of infertility are ovulatory dysfunction, male factor infertility, and tubal disease. The remaining 15% of infertile couples have "unexplained infertility." Lifestyle and environmental factors, such as smoking and obesity, can adversely affect fertility. [3]

Use of gonadotropin therapy is so central to infertility treatment that it is easy to overlook the considerable discovery and research that preceded the production of the effective and safe products available today. Central to the management of anovulatory infertility is the administration of exogenous hormones to induce and regulate follicular development. Human menopausal gonadotropin (HMG), or menotropin, comprises both follicle-stimulating hormone (FSH) and luteinizing hormone (LH), crucial in stimulating ovarian follicles and supporting the maturation of oocytes. This hormonal preparation mimics the natural processes of follicular growth, essential for successful ovulation induction in women who do not produce adequate FSH and LH on their own. [4]

In conjunction with HMG, human chorionic gonadotropin (hCG) plays a pivotal role in triggering final oocyte maturation and initiating the ovulation process. The strategic use of hCG in controlled ovarian stimulation protocols not only ensures timed follicular maturation but also mitigates risks such as ovarian hyperstimulation syndrome through precise monitoring and dosage adjustments. In addition, a number of trials carried out over the past decade have described data supporting the use of hCG for ovarian stimulation in assisted reproductive technologies (ARTs), suggesting a role in folliculogenesis. [5,6]

While international guidelines provide general recommendations for gonadotropin use, the unique genetic, environmental, and socioeconomic factors in India necessitate a tailored approach. [7] Furthermore, the rapid evolution of

ART practices and the introduction of new pharmaceutical formulations require continuous reassessment of clinical protocols. [8]

This study employs a questionnaire-based survey conducted among fertility specialists across India to gather insights into their clinical practices and perspectives on the use of HMG and hCG in IVF. By exploring physicians' experiences, dosing preferences, and monitoring techniques, the study aims to evaluate the efficacy and safety of these protocols in real-world settings within the Indian healthcare context. Insights gained from this research are expected to contribute valuable data that can inform clinical decision-making, optimize treatment outcomes, and ultimately enhance reproductive care for individuals seeking fertility interventions in India.

2 RATIONALE OF THE STUDY

The rationale for this study is to evaluate the efficacy, dosing strategies, and clinical outcomes of HMG and hCG protocols IVF among Indian patients. By understanding current prescribing practices and clinical experiences, the study aims to optimize treatment protocols and improve patient outcomes in ART.
The purpose of this study is to gather insights into the clinical use of HMG and hCG in IVF treatments among Indian physicians, focusing on dosing regimens, patient monitoring, and treatment outcomes.

3 STUDY OBJECTIVE

The primary objective of this study is to assess the current clinical practices and perspectives of Indian physicians regarding the use of HMG and hCG in IVF treatments.

4 METHODS

The study was a cross-sectional, questionnaire-based investigation targeting Indian physicians involved in the management of infertility. The objective was to gather detailed information about the clinical use of HMG and hCG. A total of 15 questions were designed to elicit comprehensive responses regarding the application of these medications in clinical practice.

Physicians were identified and invited to participate through professional networks and medical associations. Prior to participation, detailed information about the study was provided to all potential participants. The survey was administered electronically to ensure convenience and ease of access. Responses were collected and securely stored to maintain participant confidentiality. Following the data collection period, statistical analysis was conducted to summarize the findings and identify key trends. The results were then compiled into a comprehensive report. This report was intended for dissemination through scientific publications and/or presentations at relevant conferences, contingent upon suitability.

The target sample size for the study was 108 Indian physicians. This number was selected to ensure a diverse and representative sample, facilitating meaningful statistical analysis of the survey data.

Ethical considerations were strictly observed throughout the study. The research adhered to the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from an Independent Ethics Committee. Participants were assured of their right to withdraw from the study at any time without facing any negative consequences. Additionally, all responses were anonymized to guarantee the confidentiality of participant information.

5 RESULTS

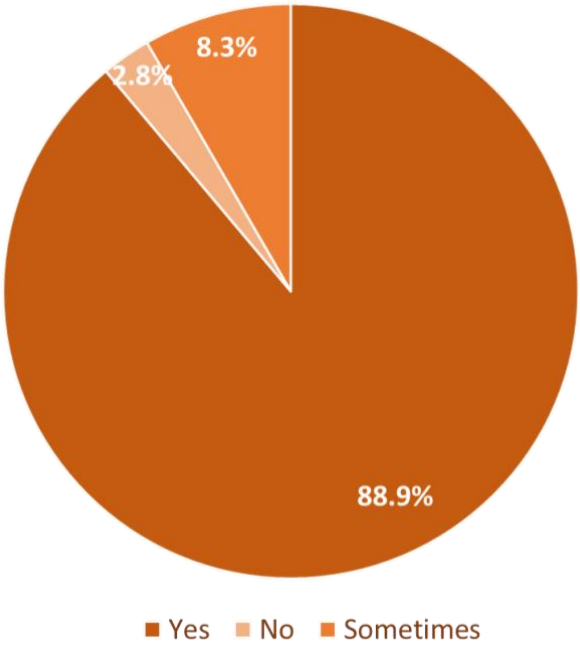
A total of 108 HCPs participated in the survey. Below is the summary of the responses.

Question 1: In your clinical practice, do you prescribe Human Menopausal Gonadotropin (HMG)/menotropin for women with anovulatory infertility?

A. Yes

B. No

C. Sometimes



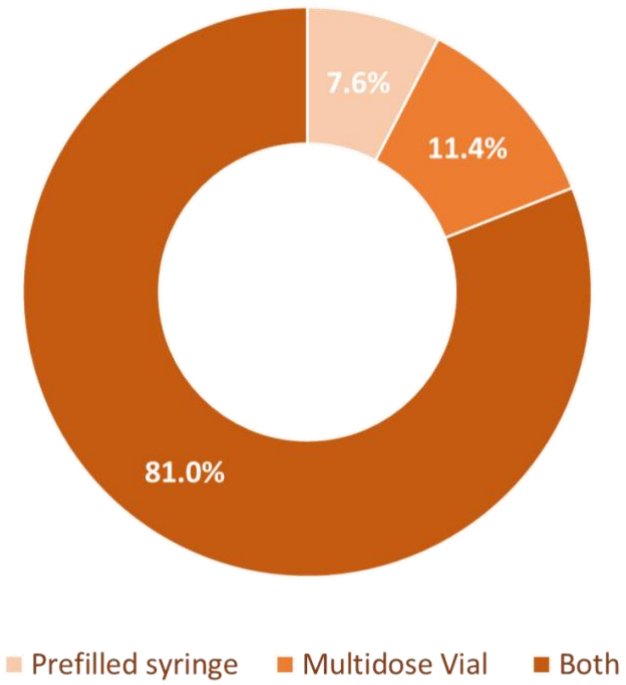
- Majority of physicians (88.9%) prescribed HMG menotropin for women with anovulatory infertility in their clinical practice.
- Approximately, 8.3% of physicians sometimes prescribed HMG menotropin for women with anovulatory infertility in their clinical practice.
- A small group (2.8%) did not prescribed HMG menotropin for women with anovulatory infertility in their clinical practice.

Question 2: In your practice, which following formulation of HMG is widely used?

A. Prefilled syringe

B. Multidose Vial

C. Both?



- Prefilled syringe and multidose vial both formulation of HMG is widely used by the majority of the physicians (81%) during their clinical practice.
- Multidose vial formulation of HMG is widely used by the 11.4% of the physicians during their clinical practice.
- Approximately 7.6% of physician used prefilled syringe formulation of HMG in their clinical practice.

Question 3: In your clinical practice, what is the recommended initial dose of HMG in patients who have received a GnRH agonist for Pituitary suppression?

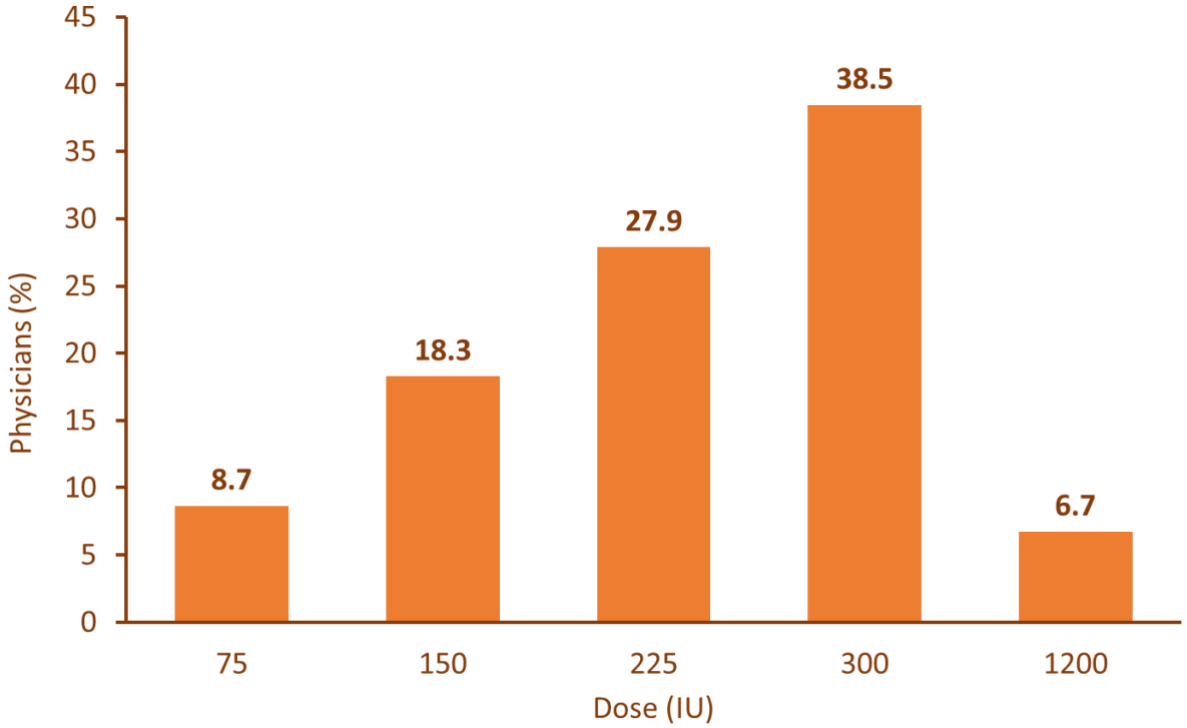
A. 75 IU

B. 150 IU

C. 225 IU

D. 300 IU

E. 1200 IU



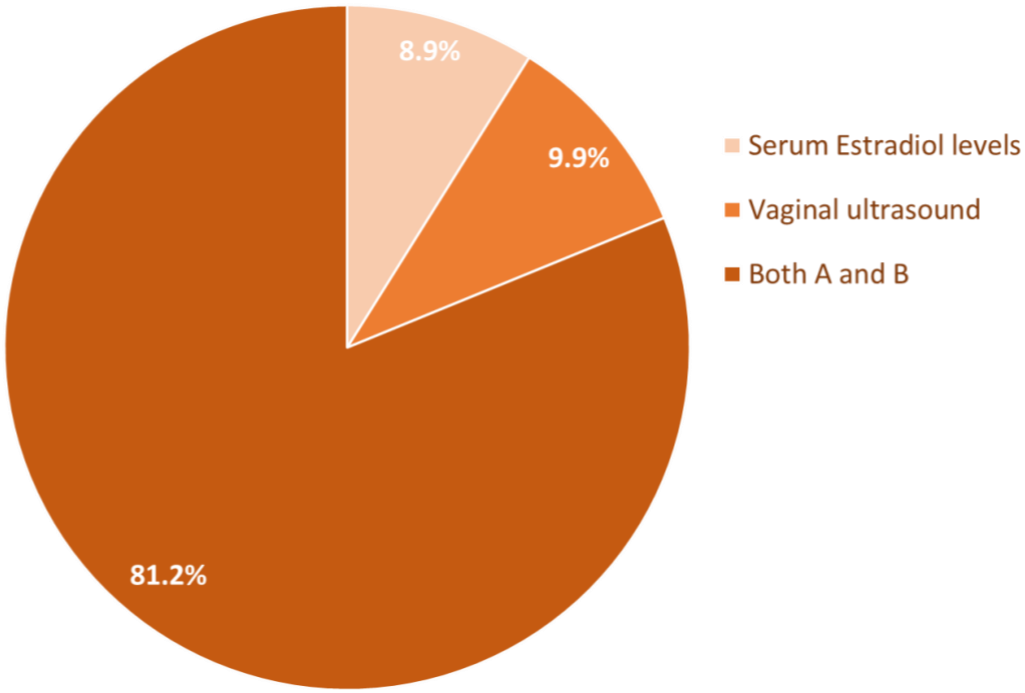
- Approximately 38.5% of physicians recommended 300 IU as initial dose of HMG in patients who have received a GnRH agonist for pituitary suppression.
- This was followed by 27.9% of physicians recommended 225 IU, 18.3% of physicians recommended 150 IU and 8.7% of physicians recommended 75 IU as initial dose of HMG in patients who have received a GnRH agonist for pituitary suppression during their clinical practice.
- Small portion of physicians (6.7%) recommended 1200 IU as initial dose of HMG in patients who have received a GnRH agonist for pituitary suppression in their clinical practice

Question 4: How do you monitor/adjust subsequent dosing of HMG in the patient?

A. Serum Estradiol levels

B. Vaginal ultrasound

C. Both A and B



- The majority of physicians (81.2%) monitored subsequent dosing of HMG in their patients by measuring both serum estradiol levels and vaginal ultrasound.
- Approximately 9.9% of physicians monitored subsequent dosing of HMG in their patients by using vaginal ultrasound.
- This was followed by 8.9% of physicians monitored subsequent dosing of HMG in their patients by measuring serum estradiol levels.

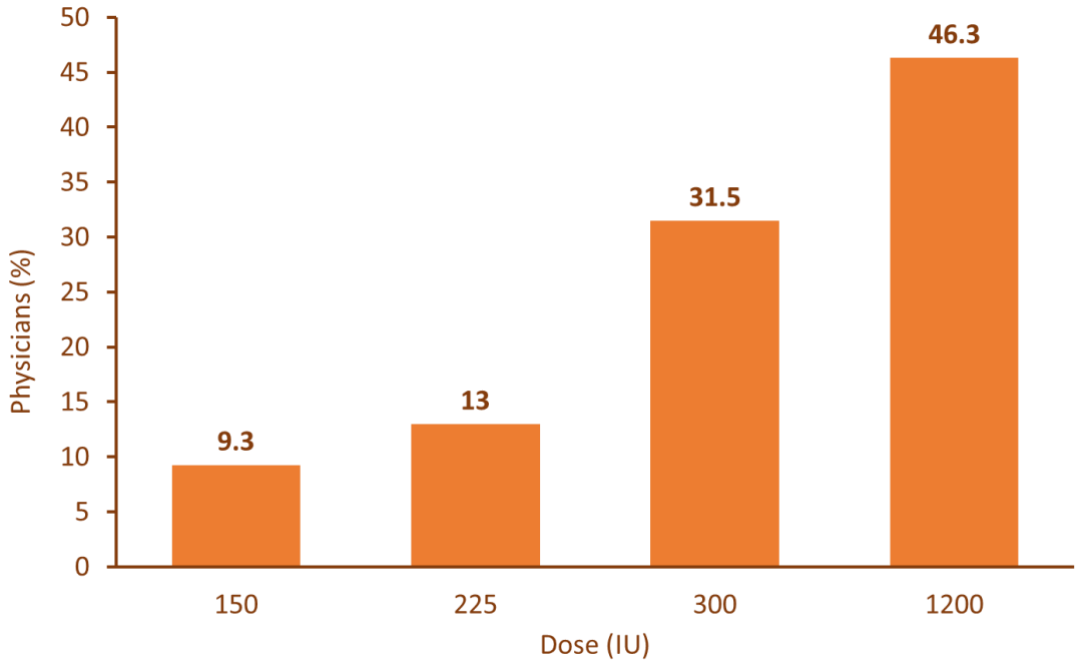
Question 5: In your practice, what is the maximum daily dose of HMG that you use in your patients?

A. 150 IU

B. 225 IU

C. 300 IU

D. 450 IU



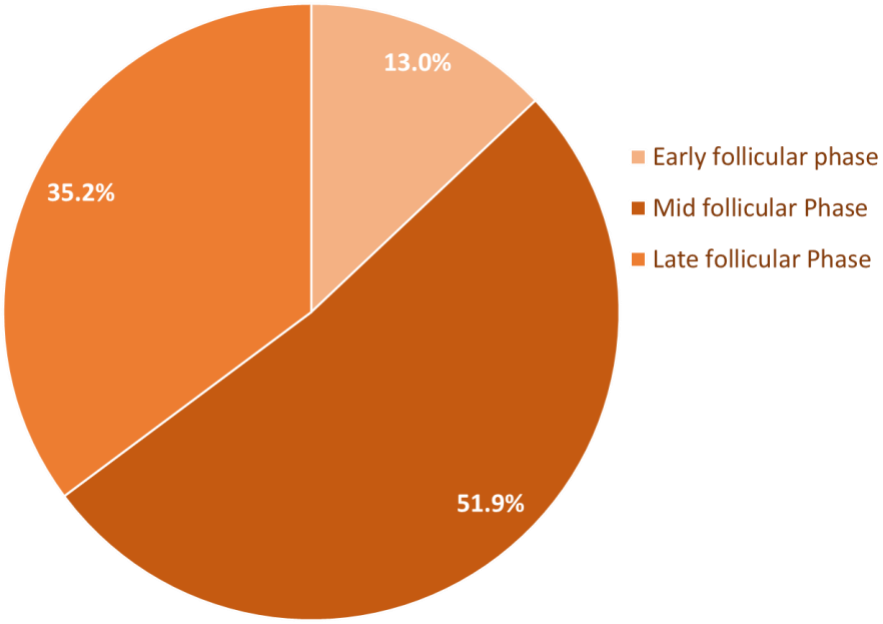
- Approximately 46.3% of physicians prescribe a maximum daily dose of 1200 IU of HMG for their patients.
- Additionally 31.5% of physicians prescribe a maximum daily dose of 300 IU of HMG for their patients.
- This was followed by 13% of physicians prescribe 225 IU and 9.3% of physicians prescribe 150 IU as maximum daily dose for HMG patients.

Question 6: In which of the following phase do you prefer low-dose human chorionic gonadotropin (hCG) in patients who are already on HMG and progesterone? (You can select multiple options)

A. Early follicular phase

B. Mid follicular Phase

C. Late follicular Phase



- Majority of physicians (51.9%) preferred administering low-dose hCG during the mid-follicular phase for patients who are already receiving HMG and progesterone.
- About 35.2% of physicians preferred administering low-dose hCG during the Late follicular Phase for patients who are already receiving HMG and progesterone.
- Approximately, 13% of physicians preferred administering low-dose hCG during the Early follicular phase for patients who are already receiving HMG and progesterone.

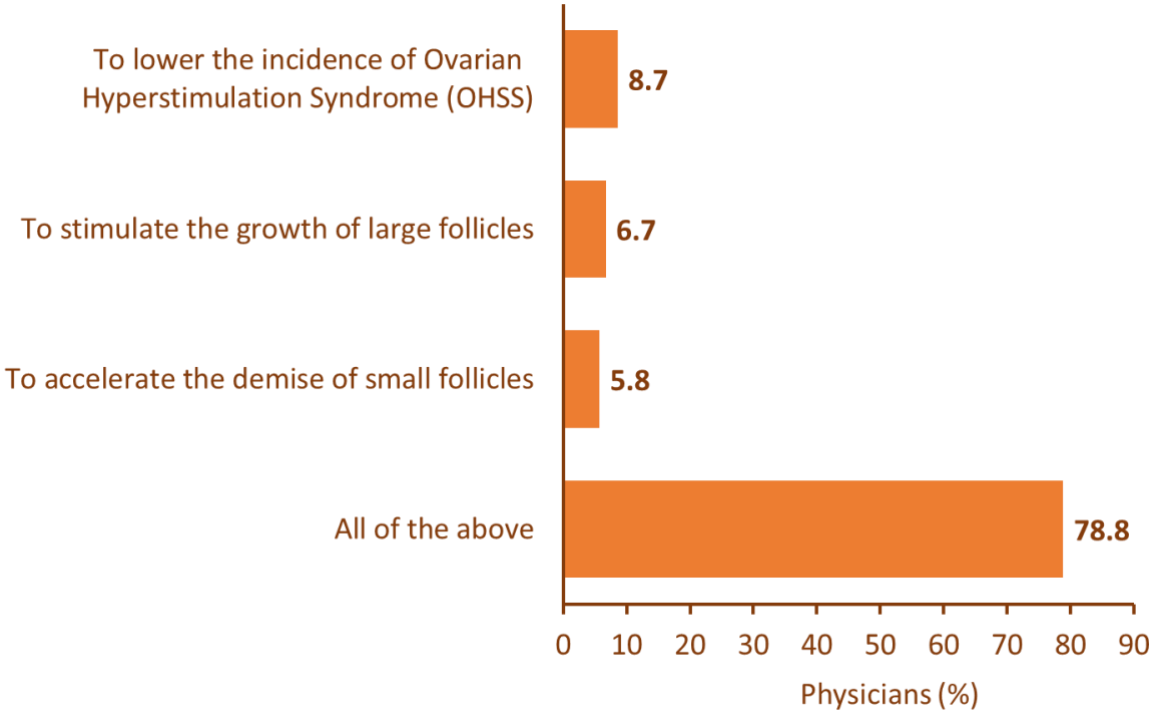
Question 7: What is the purpose of using low dose HCG in mid or late follicular phase?

A. To stimulate the growth of large follicles

B. To accelerate the demise of small follicles (<10mm diameter)

C. To lower the incidence of Ovarian Hyperstimulation Syndrome (OHSS)

D. All of the above



- To stimulate the growth of large follicles, to accelerate the demise of small follicles (<10mm diameter) and to lower the incidence of OHSS was the purpose of majority of physicians (78.8%) for using low dose HCG in mid or late follicular phase.
- To lower the incidence of OHSS was the only purpose of 8.7% of physicians for using low dose HCG in mid or late follicular phase.
- To stimulate the growth of large follicles was the only purpose of 6.7% of physicians for using low dose HCG in mid or late follicular phase.
- To accelerate the demise of small follicles (<10mm diameter) was the only purpose of 6.7% of physicians for using low dose HCG in mid or late follicular phase.

Question 8: What is the most preferred dose of hCG in mid/late follicular phase?

A. 50 IU

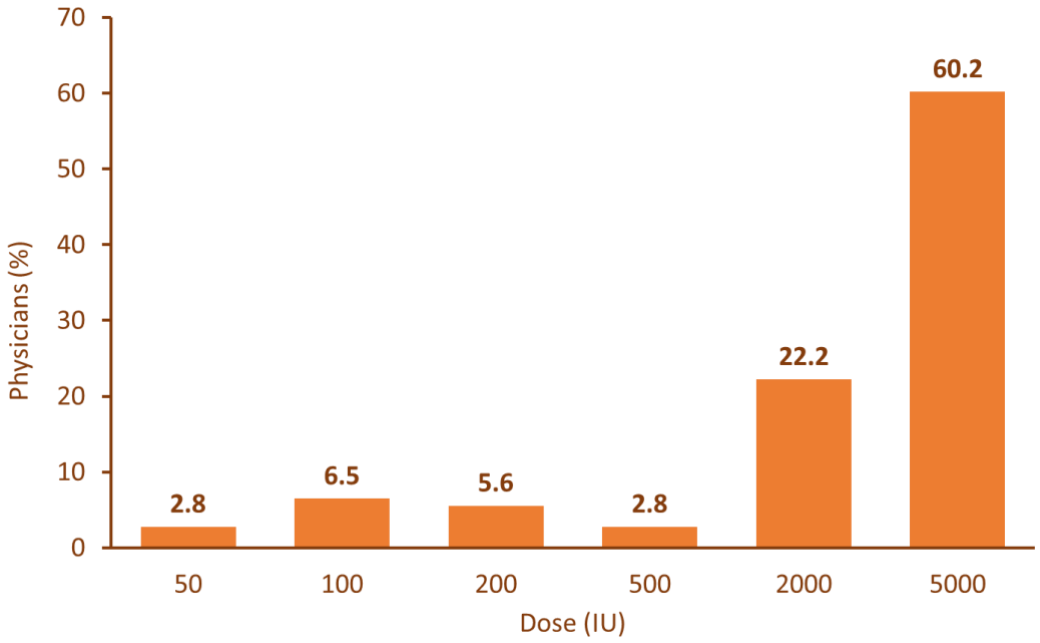
B. 100 IU

C. 200 IU

D. 500 IU

E. 2000 IU

F. 5000 IU



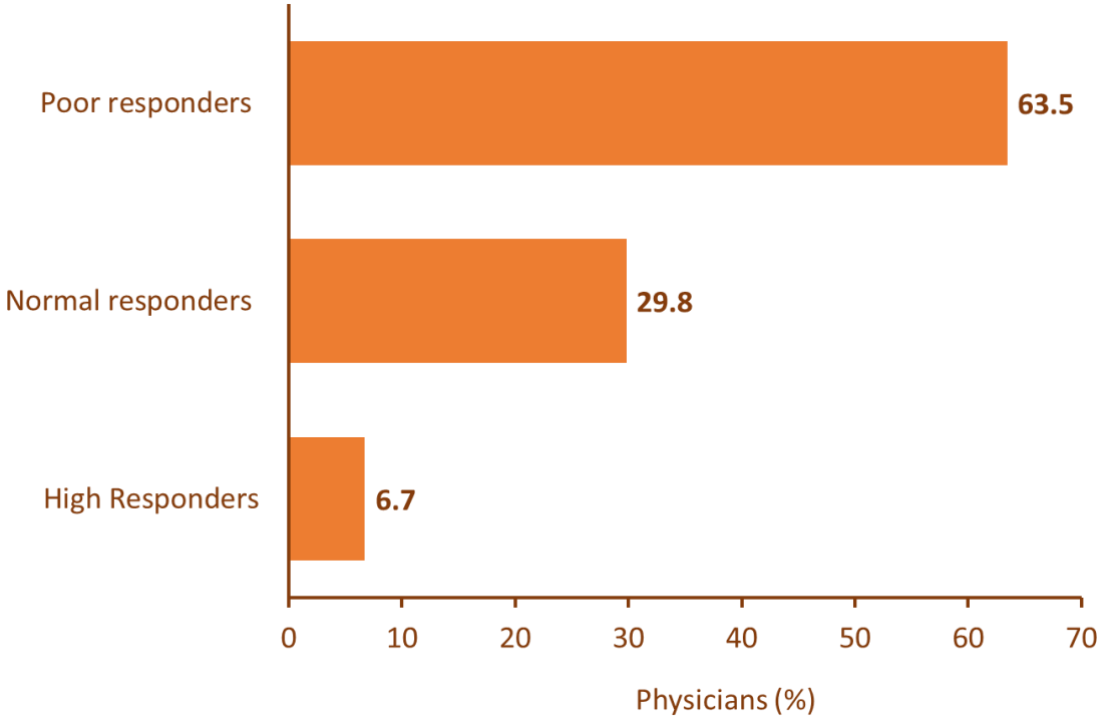
- Majority of physicians (60.2%) preferred 5000 IU dose of hCG in mid/late follicular phase.
- This was followed by 22.2% preferred 2000IU , 6.5% preferred 100 IU and 5.6% preferred 200 IU dose of hCG in mid/late follicular phase.
- A small portion of physicians 2.8% preferred 500 IU dose of hCG in mid/late follicular phase.
- Similarly, 2.8% of physicians preferred 50 IU dose of hCG in mid/late follicular phase.

Question 9: In which type of patients do you prefer HMG with HCG protocol? (you may select multiple options)

A. Poor responders

B. Normal responders

C. High Responders



- Majority of physicians (63.5%) preferred the HMG with hCG protocol for poor responders, while 29.8% prefer it for normal responders.
- Approximately, 6.7% of physicians preferred the HMG with hCG protocol for high responders.

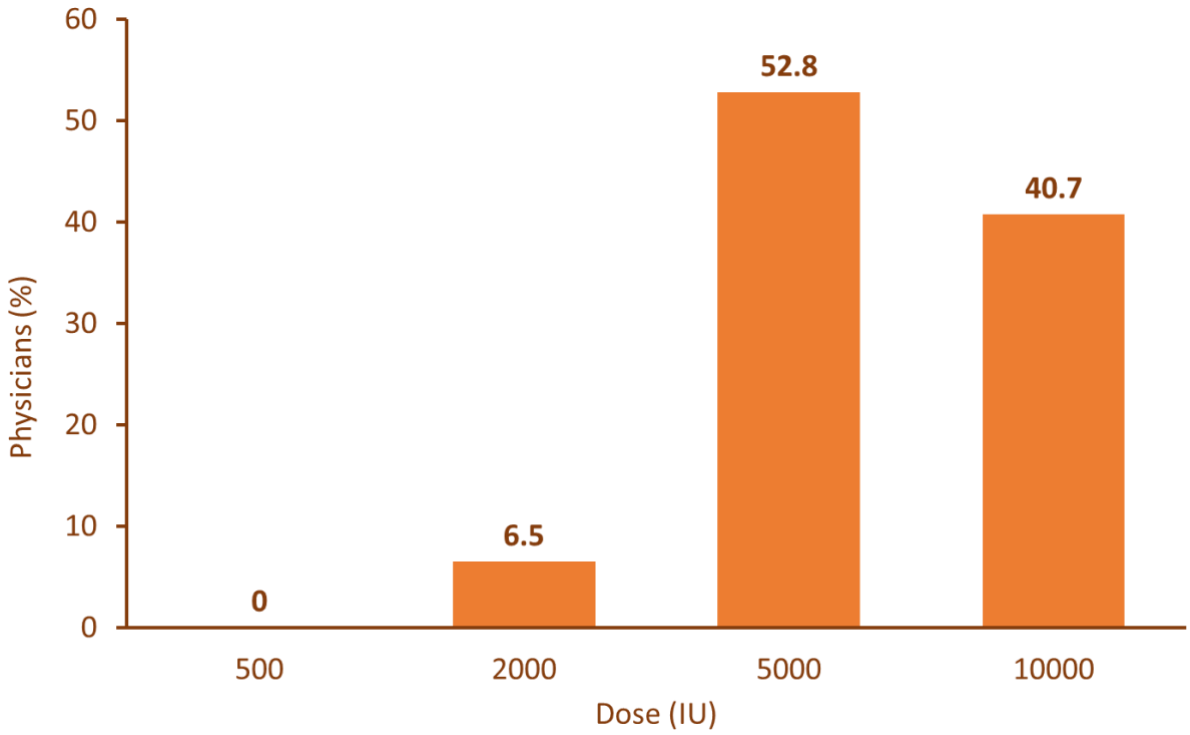
Question 10: What is the preferred dose of hCG in anovulatory women taking HMG?

A. 500 IU

B. 2000 IU

C. 5000 IU

D. 10000 IU

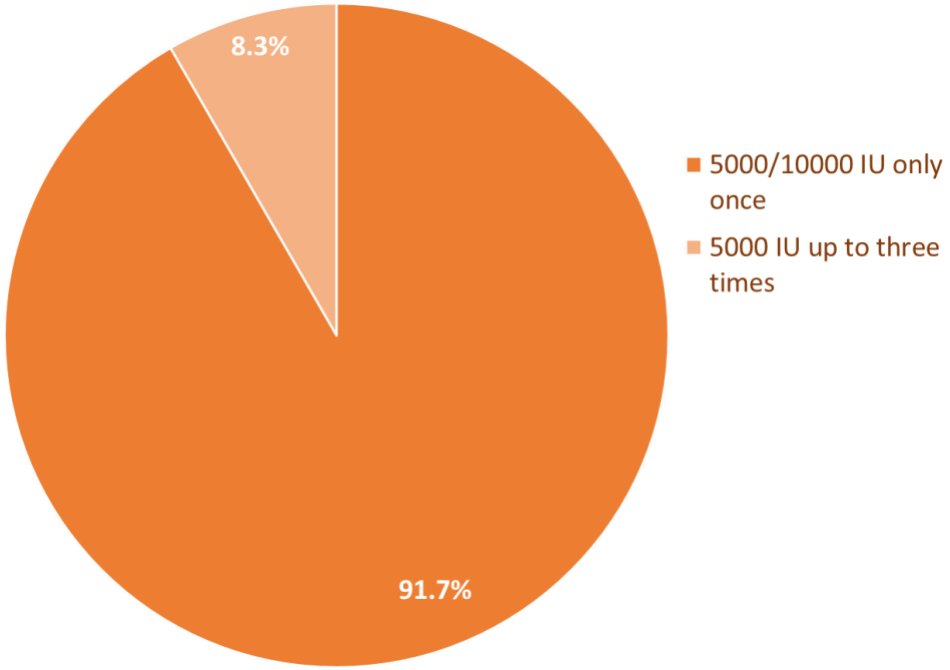


- Majority of physicians preferred 5000 IU of dose for hCG in anovulatory women taking HMG during their clinical practice.
- Approximately. 40.7% of physicians preferred 10000 IU of dose for hCG in anovulatory women taking HMG during their clinical practice.
- About 6.5% of physicians preferred 2000 IU of dose for hCG in anovulatory women taking HMG during their clinical practice.
- No physicians preferred 500 IU of dose for hCG in anovulatory women taking HMG during their clinical practice.

Question 11: How frequently is hCG given in anovulatory women on HMG? (you may select more than one option)

A. 5000/10000 IU only once

B. 5000 IU up to three times

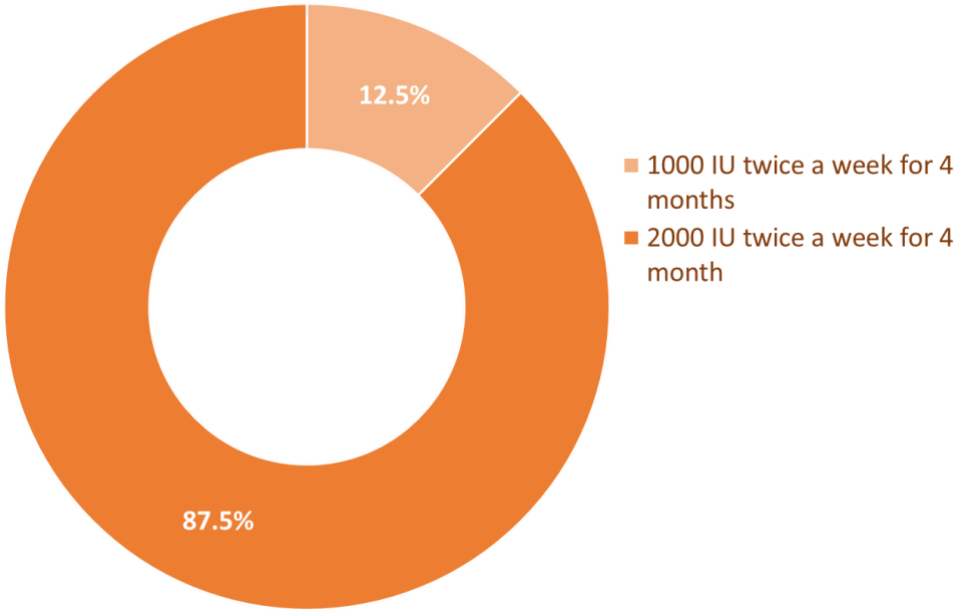


- Majority of physicians (91.7%) preferred hCG 5000/10000 IU only once to anovulatory women on HMG.
- Approximately, 8.3% of physicians preferred hCG 5000 IU up to three times to anovulatory women on HMG.

Question 12: What is the dosing & frequency of hCG used for hypogonadotropic hypogonadism in male patients on HMG?

A. 1000 IU twice a week for 4 months

B. 2000 IU twice a week for 4 months



- Majority of physicians, (87.5%) used a dosing regimen of 2000 IU of hCG twice a week for 4 months in male patients with hypogonadotropic hypogonadism who are on HMG.
- Around 12.5% of physicians used a dosing regimen of 1000 IU of hCG twice a week for 4 months in male patients with hypogonadotropic hypogonadism who are on HMG.

Question 13: For ovulation induction with HMG, hCG is usually administered when two or more ovarian follicles reached a mean diameter of _____

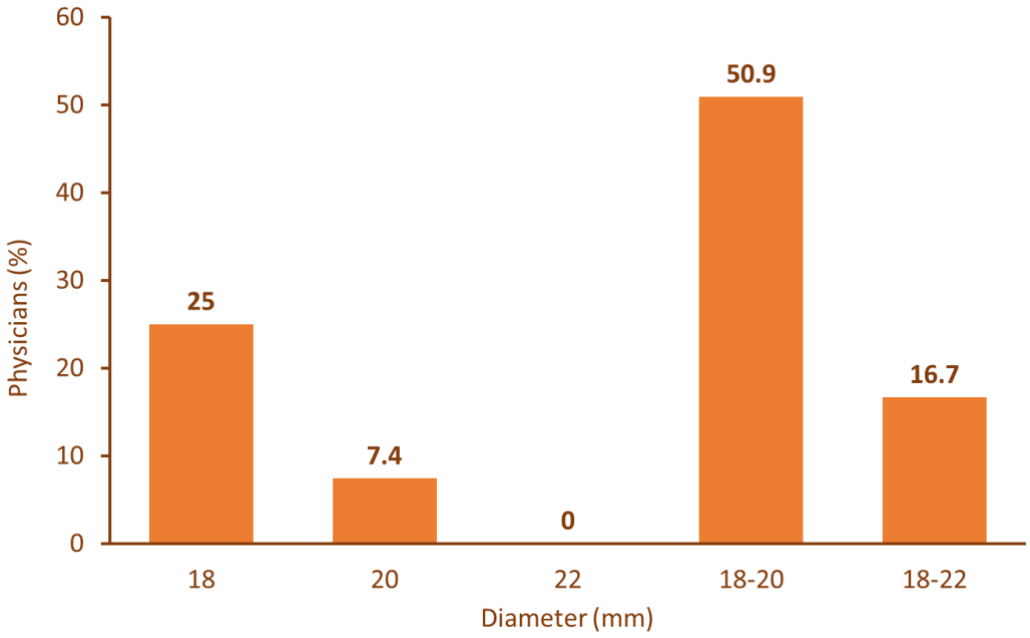
A. 18 mm

B. 20 mm

C. 22 mm

D. 18-20 mm

E. 18-22 mm

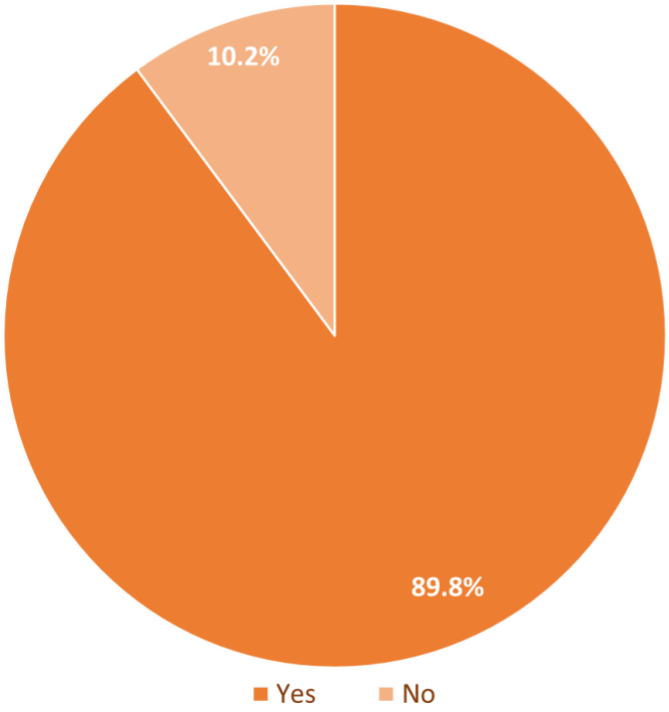


- Majority of physicians (50.9%),reported that hCG is usually administered for ovulation induction with HMG when two or more ovarian follicles reach a mean diameter of 18-20 mm.
- According to 25% of physicians, hCG is usually administered for ovulation induction with HMG when two or more ovarian follicles reach a mean diameter of 18 mm.
- Approximately, 16.7 % of physicians, hCG is usually administered for ovulation induction with HMG when two or more ovarian follicles reach a mean diameter of 18-22 mm.
- Around, 7.4 % of physicians, hCG is usually administered for ovulation induction with HMG when two or more ovarian follicles reach a mean diameter of 20 mm.
- No physicians reported on the mean diameter of 22 mm.

Question 14: In the past, have you used Materna HCG in your practice?

A. Yes

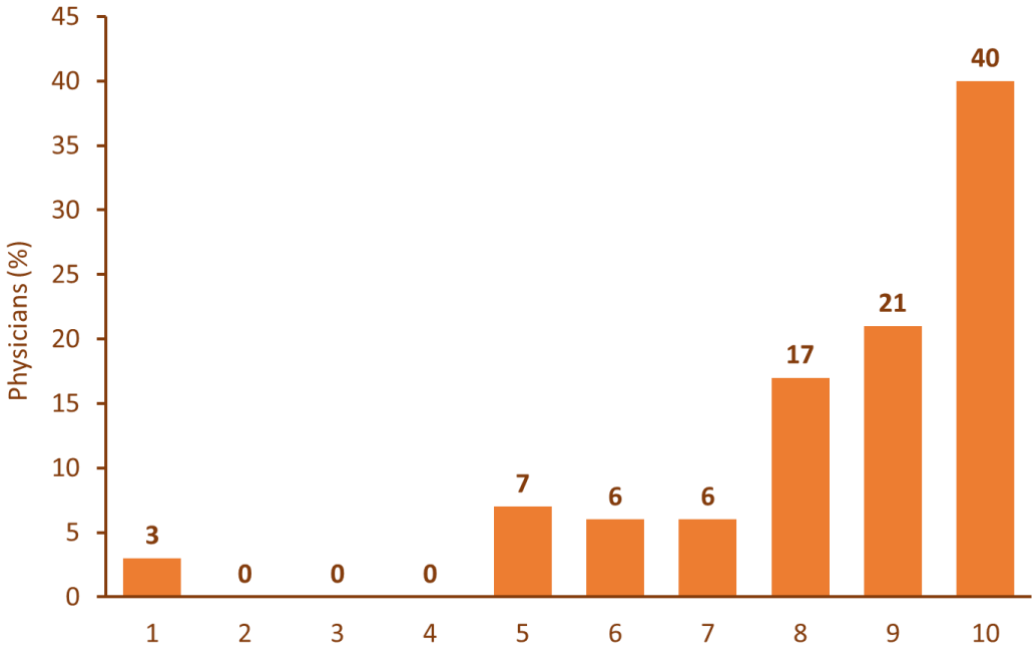
B. No



- Majority of physician (89.8%) used materna HCG in past for their clinical practice. In contrast 10.2% of physicians does not used materna HCG in past for their clinical practice.

Question 15: If yes, how would you rate your experience (in terms of efficacy & safety) with Materna HCG on a scale of 1-10 (1 being worst, 10 being best)?

1	2	3	4	5	6	7	8	9	10



The experience with Materna HCG in terms of efficacy and safety is rated as follows:

- Majority of the physicians (40%) rate their experience as the best possible 10, indicating high satisfaction with the product.
- Additionally, 21% rate it as 9, and 17% rate it as 8 reflecting strong positive feedback.
- Lower ratings are less common, with 6% rating it as 7 again 6% rating it as 6 and 7% rating it as 5. Only a 3% rate it as 1.
- No physicians responded on the range of 2-4. Suggesting that while some dissatisfaction exists, the majority of physicians report a favorable experience with Materna hCG.

6 SUMMARY

The survey revealed that a significant majority of physicians (88.9%) regularly prescribed HMG menotropin for anovulatory infertility, with only a small fraction (2.8%) not prescribing it at all. Among those who did, both Prefilled Syringe and Multidose Vial formulations were commonly used, though Multidose Vial was slightly more prevalent. Physicians varied in their initial dosing recommendations of HMG for patients on GnRH agonists, with the majority recommending 300 IU. Most physicians (81.2%) monitored treatment progress using both serum estradiol levels and vaginal ultrasound.

For maximum daily doses, 46.3% of physicians prescribed 1200 IU of HMG, while a notable portion (31.5%) opted for 300 IU. Low-dose hCG administration strategies varied, with 51.9% preferring the mid-follicular phase and 35.2% the late follicular phase. The majority (60.2%) chose a 5000 IU dose of hCG for the mid/late follicular phase. The HMG with hCG protocol was favored for poor responders by 63.5% of physicians, with 5000 IU being the most preferred dose for anovulatory women.

In male patients with hypogonadotropic hypogonadism, 87.5% used a 2000 IU hCG dosing regimen twice a week. When administering hCG for ovulation induction with HMG, most physicians (50.9%) targeted follicles reaching 18-20 mm in diameter. Materna hCG was used by 89.8% of physicians, with most rating their experience positively, although a small percentage expressed dissatisfaction. This feedback suggests a generally favorable view of Materna hCG's efficacy and safety.

7 DISCUSSION

The survey provided insightful data on the clinical use of HMG and hCG among Indian physicians managing infertility. A significant majority (88.9%) of physicians prescribed HMG menotropin for women with anovulatory infertility, reflecting its prominent role in treatment regimens. While a small group (2.8%) did not prescribe it, a minority (8.3%) reported occasional use, suggesting variability in clinical practice or patient needs. Regarding HMG formulations, most physicians (81%) utilized both prefilled syringes and multidose vials, indicating flexibility in administration options. However, a clear preference

emerged, with 11.4% favoring multidose vials and 7.6% preferring prefilled syringes. The choice of HMG formulation may depend on practical considerations and patient preferences.

The survey revealed variability in initial dosing of HMG following GnRH agonist treatment. A notable portion (38.5%) recommended 300 IU, while smaller percentages recommended 225 IU, 150 IU, or 75 IU. A minority (6.7%) suggested a higher initial dose of 1200 IU. This variation underscores the lack of consensus on optimal dosing strategies in clinical practice.

Monitoring practices varied among physicians, with the majority (81.2%) using both serum estradiol levels and vaginal ultrasound to track HMG dosing, reflecting a comprehensive approach. A smaller group relied on either ultrasound (9.9%) or estradiol levels (8.9%) alone, highlighting diverse monitoring preferences.

Dosing regimens also differed, with 46.3% prescribing a maximum daily dose of 1200 IU and 31.5% opting for 300 IU. Lower doses of 225 IU and 150 IU were less commonly prescribed. These variations suggest that dosing decisions are tailored to individual patient needs and response. The timing and dosing of hCG administration also showed considerable variation. Most physicians (51.9%) preferred administering low-dose hCG during the mid-follicular phase, while 35.2% chose the late follicular phase. The primary objectives for using low-dose hCG included stimulating large follicle growth and reducing OHSS incidence. A majority (60.2%) preferred a 5000 IU dose, though preferences ranged from 50 IU to 5000 IU, indicating a lack of uniformity in practice. For the HMG with hCG protocol, 63.5% favored it for poor responders, while 29.8% used it for normal responders, and 6.7% for high responders. This choice reflects individualized treatment strategies based on patient response.

In treating anovulatory women with HMG, most physicians preferred administering hCG in doses of 5000 IU or 10000 IU, with a majority (91.7%) recommending it only once. The preference for 5000 IU hCG aligns with clinical practice trends. For male patients with hypogonadotropic hypogonadism, 87.5% used a regimen of 2000 IU of hCG twice a week for 4 months, illustrating a common approach to treatment. Regarding the timing of hCG administration for

ovulation induction, a majority (50.9%) preferred a mean follicle diameter of 18-20 mm, while others chose slightly different thresholds. Finally, a high proportion of physicians (89.8%) had used Materna hCG in their practice. The majority reported high satisfaction, with 40% rating their experience as excellent. This suggests strong overall confidence in the product's efficacy and safety.

8 CLINICAL RECOMMENDATIONS

- HMG Menotropin Usage: The majority of physicians (88.9%) prescribe HMG menotropin for anovulatory infertility. This suggests it is the preferred treatment option for this condition.
- Formulations of HMG: Prefilled syringes and multidose vials of HMG are widely used, with prefilled syringes being more common among physicians (81%). Physicians should continue using these formulations based on their clinical preference and patient needs.
- Initial Dose of HMG: The recommended initial dose of HMG for patients receiving GnRH agonists varies, with 38.5% suggesting 300 IU. Physicians should consider starting with this dose and adjusting as necessary based on patient response.
- Monitoring Subsequent Dosing: Most physicians (81.2%) use both serum estradiol levels and vaginal ultrasound to monitor HMG dosing. This dual monitoring approach should be maintained for comprehensive patient evaluation.
- Maximum Daily Dose: A substantial proportion of physicians (46.3%) prescribe a maximum daily dose of 1200 IU of HMG. This dose is recommended for effective treatment while minimizing the risk of ovarian hyperstimulation syndrome (OHSS).
- Administration of Low-Dose hCG: The preferred timing for administering low-dose hCG is mid-follicular phase (51.9%). This approach should be adopted to stimulate follicle growth and manage OHSS risk.
- hCG Dosage: A majority (60.2%) prefer a 5000 IU dose of hCG in the mid/late follicular phase. This dosage should be considered the standard practice for optimizing treatment outcomes.

- Protocol Preferences: The HMG with hCG protocol is favored for poor responders (63.5%). Physicians should continue using this protocol for managing patients with a lower response to fertility treatments.
- Materna HCG Experience: The majority of physicians report high satisfaction with Materna hCG, with 40% rating it as the best possible. Continued use of Materna hCG is recommended based on its positive efficacy and safety profile.
- Specific Considerations: Physicians should tailor the dosage and treatment regimens based on individual patient responses and clinical scenarios to ensure optimal outcomes.

9 CONSULTANT OPINION

The survey revealed that the majority of physicians (88.9%) routinely prescribe HMG menotropin for anovulatory infertility, with 81% utilizing both prefilled syringes and multidose vials. The common initial dose of HMG is 300 IU, and most physicians monitor treatment via both serum estradiol and vaginal ultrasound. Low-dose hCG is predominantly administered during the mid-follicular phase, with 5000 IU being the favored dose. A significant majority reported high satisfaction with Materna hCG, indicating its effectiveness and safety in clinical practice.

10 MARKET OPPORTUNITIES

- The survey studied significant marketing opportunities for HMG and hCG products, particularly Materna hCG. The majority of physicians (88.9%) routinely prescribe HMG menotropin for anovulatory infertility, indicating a strong market for related medications.
- The preference for both prefilled syringes and multidose vials suggests that offering flexible formulation options could capture a larger share of the market.
- Notably, 81.2% of physicians monitor dosing with both serum estradiol levels and vaginal ultrasound, highlighting the need for products compatible with comprehensive monitoring practices.

- Additionally, the high satisfaction rates with Materna hCG, where 40% of physicians rate it as the best possible, presents an opportunity to emphasize product efficacy and safety in marketing efforts.
- The diverse dosing preferences and protocols for administering hCG further suggest targeted strategies to address specific physician practices and preferences, enhancing the product's appeal across varying clinical scenarios.

11 MARKET POSITIONING

The survey results reveal a prominent market positioning for HMG and hCG in infertility treatment among Indian physicians. A significant majority (88.9%) of physicians consistently prescribe HMG menotropin for anovulatory infertility, demonstrating its strong presence in clinical practice. The preference for HMG formulations shows that 81% of physicians use both prefilled syringes and multidose vials, with the multidose vial being more commonly utilized (11.4%) compared to the prefilled syringe (7.6%).

When it comes to dosing, 38.5% of physicians prefer an initial dose of 300 IU of HMG for patients who have received a GnRH agonist for pituitary suppression, with varying preferences for lower doses also noted. For monitoring, the majority (81.2%) employ both serum estradiol levels and vaginal ultrasound to track dosing, while a smaller segment relies on individual methods.

Regarding hCG administration, 60.2% of physicians favor a 5000 IU dose in the mid/late follicular phase, highlighting its dominance over other dosages. The protocol for poor responders is favored by 63.5% of physicians, underscoring the efficacy of the HMG with hCG regimen.

In terms of hCG dosing for anovulatory women, a clear preference for 5000 IU (91.7%) and 10000 IU (40.7%) indicates a strong inclination towards higher doses. Most physicians (87.5%) also prefer a dosing regimen of 2000 IU of hCG twice a week for hypogonadotropic hypogonadism in male patients.

Experience with Materna hCG has been rated favorably by 78% of physicians, with 40% giving it the highest satisfaction rating. This reflects a robust market position of Materna hCG, despite some variability in feedback..

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