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Egyptian Foundation of Reproductive Medicine and Embryology Survey for Luteal Support in IVF among Fertility Specialists

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Abstract

Background: The currently used protocols for luteal phase support during IVF are variable among centers. In certain areas, the practice is neither evidence based nor guidelines driven.

Objective: **to evaluate practitioners' preferences and extent of deviation from current** evidence**.**

Methods: A survey was designed using Google Forms. Invitations were sent via 1341 emails and 110 WhatsApp links.

Results: 120 responded to questionnaires (8.27%). In fresh cycles, 81.5% of participants did not individualize LPS protocol based on evidence alone; they rather considered patient preferences. The dose of vaginal progesterone used is (≥ 600 mg). 78% of national participants use combination of vaginal route with IM either daily or every 3 days, however, the international participants prefer to use IM/3 days. In frozen cycles, 75% of national and international participants did not use vaginal progesterone alone. The most deviant from guidelines was that 32.7% of Egyptian participants use estrogen for luteal support in antagonist cycles. In Fresh cycles, 60% of Egyptian participants continued LPS beyond 8 weeks while no one of the international participants does. Whereas in frozen cycles, 50% of international experts used a different policy of continuing LPS beyond 8 weeks.

Conclusion: Individualization of LPS protocol needs more consideration as apparently, the practice is not individualized and not adherent to guidelines in the progesterone dose, formulation and when to stop LPS. The practice of vaginal progesterone alone is declining. Unjustifiable high doses and long duration of progesterone are used. The empiric use of estradiol and oral progestin should be audited.

Keywords: Luteal phase support, Progesterone, IVF, Survey.

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Debate

Introduction

In normal pregnancy, the Corpus Luteum (CL) supports pregnancy for up to 8 gestational weeks (1). ART cycles, however, are associated with luteal phase deficiency and must be pharmaceutically supported (2). Luteal phase support (LPS) is fundamental to overcoming the defect in the luteal phase between the disappearance of hCG, from triggering, till the initiation of endogenous hCG from the conceptus (3). Progesterone constitutes the main component of LPS for ART (4). There is no consensus about formulation, route of administration, timing, and combination of drugs that should be used in LPS regimens.

In 2014, a patient administration preference survey was published showing that the vaginal route of administration was easier, more convenient, and satisfactory compared to intramuscular methods (70% vs. 18%). Clinical and ongoing pregnancy rates were comparable in both groups (5).

Evidence concerning LPS remains inconclusive in many aspects due to the low quality of the studies tackling the subject (6). In 2020, the results of a survey completed by 148 clinicians from 34 countries were published showing that 80% of clinicians used vaginal progesterone only, whereas 6% prescribed intramuscular progesterone. Oral progestin and subcutaneous progesterone were used by only 5% of the participating physicians. Progesterone was administered till 8–10 weeks' gestation by 35%, whereas 52% of respondents continued LPS until 12 weeks (7). In 2021, the results of a 10-year follow-up survey were published showing that in fresh cycles, vaginal progesterone was the principal delivery route in 74.1% of participating centers. The authors pointed out that the quality of evidence and level of recommendations were surprisingly low for most topics. There was no single accepted LPS protocol, and it has been clear that real-life practice is still different from evidence (8).

The homogeneity of decisions shared by patients and practitioners was challenged by a recently published article by Devine et al in favor of intramuscular progesterone. The live birth rate after administration of vaginal-only progesterone was significantly reduced (29%) (9), primarily due to an increased miscarriage rate. Vaginal progesterone with intramuscular progesterone every third-day supplementation was not inferior to daily intramuscular progesterone alone (48% and 46% respectively). The main differences between fresh and frozen embryo transfer cycles are the physiological changes, Therefore, the luteal support as a concept should be adjusted consequently (10). GnRH agonists and oral dydrogesterone are novel and promising treatment modalities. Yet, more research is required (11). Currently, hCG and estradiol are not recommended for luteal phase support (12).

Materials and Methods

Study design

The EFRE survey was designed using Google Forms. The form enables access to a large number of clinicians and IVF clinics all over the world to gather different opinions. That was the first time in Egypt to do such a survey. It is a cross-section study. The results of the survey were based on thousands of ART cycles conducted in different IVF centers represented by their leadership in the Egyptian Foundation of Reproductive Medicine and Embryology (EFRE) and EFRE 2022 international conference in Cairo as well as international speakers attending the conference.

Participants

Invitations to participate in the survey were first emailed to a sample of IVF physicians in the EFRE organization. Then, it was sent to a larger number of IVF physicians; 1341 emails were sent in addition to 110 WhatsApp links. The survey was launched 10 days before the conference. Then, in the panel of LPS at the 2nd annual conference, the survey was available through scanning of a QR code.

The link for the survey was https://docs.google.com/forms/d/e/1FAIpQLSfSyyDVazu6V8WPshVcvLteXUDzC_ZhNoQx-pYQDk6CUOWz_w/viewform?usp=sf_link.

To make sure that everyone has submitted only one entry, we selected the option "limit to one response" from the settings and used the "remove the duplicate feature on excel" to make sure no answers were duplicated. So the complete duplicates were removed.

General Data Protection Regulation (GDPR)

Our survey was conducted in agreement with the GDPR privacy policy. By default, Google Forms does not collect email addresses. This allowed respondents to respond anonymously and fill out the form without a need for a Google account. The data was not shared with any third parties.

Results

The survey was sent through 1341 emails in addition to 110 WhatsApp links. 120 returned completed questionnaires yielding a response rate of 8.27%. The respondents were 110 clinicians from Egypt and 10 international speakers.

Survey questions were divided into two main sections:

a. Questions related to fresh ET cycles,
b. b. Questions related to frozen ET cycles

A. Fresh cycles (Q1-16)

Question 1 (Q1) investigated the policy of ET in antagonist cycles (fresh or freeze all), interestingly less than 30% use fresh transfer in most of their cycles (Table 1). More than 60% of the participants (either national or international) started luteal support on the day of oocyte Retrieval (OR) (Q2).

Most participants (81.5%) did not individualize their LPS protocol, in fresh cycles, based on evidence alone (Q4). There was no agreement on individualizing LPS according to the Stimulation Protocol (Q6) and response (Q7). However, 30% used individualized LPS. Concerning the route of administration, less than 20% of Egyptian participants used vaginal methods alone compared to 50% of international participants (Q8, figure 1). Most of the national participants (78%) used a combination of vaginal and IM methods either daily (40%) or every three days (38%). Only 40% of international participants used the combination with IM/3 days (Q9).

The most used form of vaginal progesterone was the suppository. Only a few participants used capsules or gel (Q12). High doses of vaginal progesterone (> 600mg daily) were reported by (60%) of national and international participants (Q13). Moreover, 50% of national participants still use 100mg IM/day, in contrast to none of the international participants. About half of national participants used oral dydrogesterone in their LPS in contradiction to only 10% of international participants (Q10). The most commonly used dose of oral dydrogesterone was 20–30 mg/day (Q11). The most deviant from the guidelines was the percentage of Egyptian participants using estrogen for luteal support in antagonist cycles (Q3). Surprisingly, 69 Egyptian doctors (62.7%) used estrogen in their LPS in fresh antagonist cycles when triggered by GnRH agonists only. Whereas 36 (32.7%) of them used estrogen in all antagonist cycles. Similarly, 80% of international doctors used estrogen in LPS either in agonist-triggered or in all antagonist cycles. Concerning the time to stop LPS after pregnancy, 60% of Egyptian participants continued LPS after 8 weeks, unlike their international counterparts (Q16).

B. Frozen Cycles (Q17-38)

Table 2 illustrates examples for questions about LPS in frozen ET (FET) cycles [Q17-Q38]. In hormone replacement therapy (HRT) endometrial preparation for FET, 20–40% start progesterone once endometrium attains 7 mm, whereas most participating doctors (62% national and 50% international) wait for at least 12 days of estradiol treatment before starting progesterone (Q17). Blastocysts are transferred on day 5 or 6 by 90% of participants (Q18). Most national experts and specialists do not prefer vaginal progesterone alone, whereas 50% of international experts use it alone (Q19, figure 1). 77% of national participants used a combination of vaginal, mainly suppositories, and IM progesterone, either daily IM or every three days. International participants, on the other hand, use a combination of IM/3 days (Q20). Surprisingly, when asked for clarification on this method, 75% of national and international participants who do not use vaginal progesterone alone, 50% of them responded that it decreased the pregnancy rate (Q21 and Q22 respectively).

Egyptian participants used a high dose of progesterone. 50% used 600 or more of vaginal progesterone and 100 mg IM progesterone daily (Q27 and Q29 respectively).

Table1 : Distribution of the policy committed in Fresh cycles between national& international participants

Fresh cycles	National (No=110)		International (No=10)	
	No.	%	No.	%
Q1; What is the percentage of fresh transfer in your antagonist cycles? (>70%)	17	15.4	3	30
Q2; When do you start LPS? (on the day of OR)	70	63.6	7	70
Q3; Estrogen for LPS in fresh antagonist cycles				
➢ If triggered by GnRH agonist only.	69	62.7	6	60
➢ In all antagonist cycles.	36	32.7	2	20
Q4; LPS based on evidence only	19	17.2	3	30
Q5; Do you modify your LPS based on serum progesterone on the day of ET? (Yes)	23	20.9	1	10
Q6; Do you modify your LPS in fresh cycles according to Stimulation protocol? (NO)	61	55.4	7	70
Q7; Do you modify your LPS in fresh cycles according to patient response? (NO)	64	58	10	100
Q9; What is your favorite combination for LPS in fresh cycles?				
➢ **Vaginal+ daily IM**	44	40	0	0
➢ **Vaginal+ IM/ 3 days**	42	38	4	40
➢ **Oral added to A or B**	20	18	1	10
Q10; Do you use oral dydrogesterone in LPS in fresh cycles? (Yes)	47	42.7	1	10
Q13; Dose of Vaginal progesterone (≥600 mg).	67	60.9	6	60
Q14; What Dose of IM progesterone do you use daily				
➢ 100 mg/day IM	53	48	0	0
➢ 100mg/3 days IM	32	29	1	10
Q15; Luteal support contains subcutaneous Progesterone (Yes)	50	45.4	4	40
Q16; Do you continue LPS > 8ws gestation (Yes)	66	60	0	0

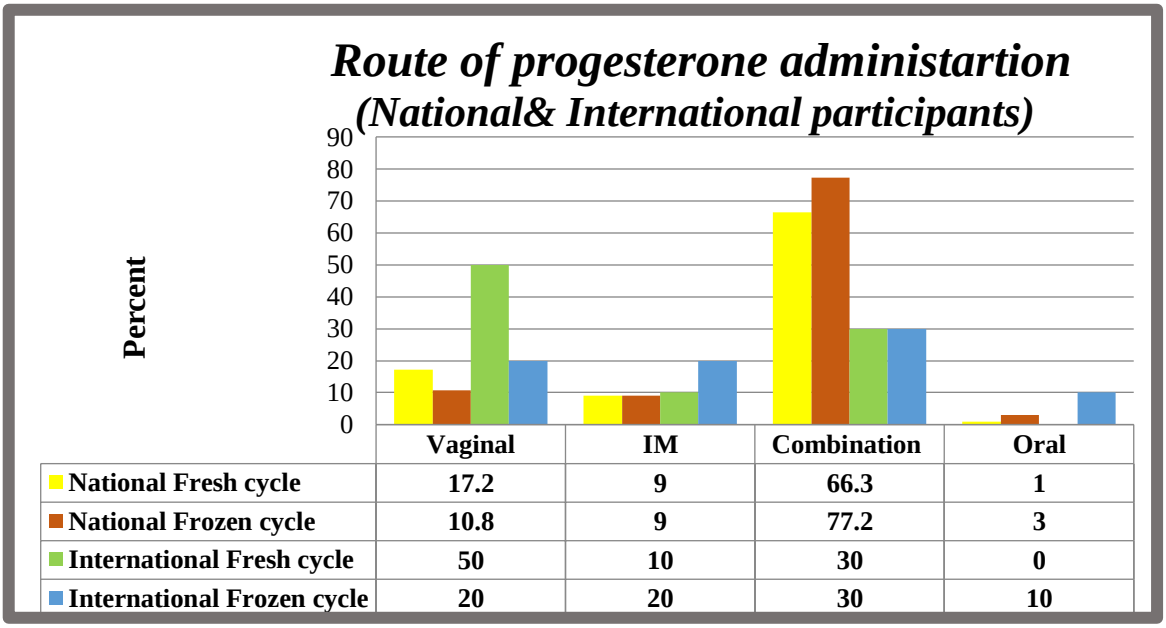
Table2 : Distribution of the policy committed in frozen cycles between national &international participants

Fresh cycles	National (No=110)		International (No=10)	
	No.	%	No.	%
Q1; What is the percentage of fresh transfer in your antagonist cycles? (>70%)	17	15.4	3	30
Q2; When do you start LPS? (on the day of OR)	70	63.6	7	70
Q3; Estrogen for LPS in fresh antagonist cycles				
➢ If triggered by GnRH agonist only.	69	62.7	6	60
➢ In all antagonist cycles.	36	32.7	2	20
Q4; LPS based on evidence only	19	17.2	3	30
Q5; Do you modify your LPS based on serum progesterone on the day of ET? (Yes)	23	20.9	1	10
Q6; Do you modify your LPS in fresh cycles according to Stimulation protocol? (NO)	61	55.4	7	70
Q7; Do you modify your LPS in fresh cycles according to patient response? (NO)	64	58	10	100
Q9; What is your favorite combination for LPS in fresh cycles?				
➢ **Vaginal+ daily IM**	44	40	0	0
➢ **Vaginal+ IM/ 3 days**	42	38	4	40
➢ **Oral added to A or B**	20	18	1	10
Q10; Do you use oral dydrogesterone in LPS in fresh cycles? (Yes)	47	42.7	1	10
Q13; Dose of Vaginal progesterone (≥600 mg).	67	60.9	6	60
Q14; What Dose of IM progesterone do you use daily				
➢ 100 mg/day IM	53	48	0	0
➢ 100mg/3 days IM	32	29	1	10
Q15; Luteal support contains subcutaneous Progesterone (Yes)	50	45.4	4	40
Q16; Do you continue LPS > 8ws gestation (Yes)	66	60	0	0

Table3: Comparison between EFRE survey& EBM

Parameter	EBM (ESHRE 2019)(14)	Previous survey 2020(7)	EFRE survey results	
			National	International
Initiation of administration	OR 0- OR+3	OR0 71% OR+1 23.6% OR+2 3.38% OR+3 2.02%	OR0 (70/110) 63.6%, OR+1 (29/110)26.3%, OR+2 (11/110)1%	OR0 (7/10) 70% OR+1 (3/10) 30%
Routes and dosage	Vaginal micronized P	600mg/d or 200/400mg/d 80%	400-600mg/d 52% ≥600 mg/d 46%	400-600mg/d 60% ≥600 mg/d 30%
	IM P 50mg/d	50- 100mg/d 6%	50-100mg/d 50% 100mg/3d 32% (in combination)	50mg/d 30% 100mg/3d 10%
	SC P 25mg/d	25mg/d 5%	25mg/d 45.5% (in combination)	25mg/d 30-40% (in combination)
	OS dydrogesterone 30mg/d	20/30mg/d 5%	20/40mg/d 42.7% (in combination)	--
	---	Combined regimen: Vag+ OS/IM 4%	Combined regimen: Vag+ OS/IM 63.3%	Combined regimen: Vag+ IM 40%, Vag+OS 10%
Discontinuation of administration	At least until the pregnancy test	PT 6% US 7% 7/8 weeks 22% 10 weeks 13% 12 weeks 52%	--- US (Fresh 16.3%, FET 11.8%) 8 weeks (Fresh 18%, FET 13.6%) 12 weeks (Fresh 60%, FET 69%)	--- US (Fresh 30%, FET 10%) 8 weeks (Fresh 70%, FET 40%) 12 weeks (Fresh 0, FET 50%)

EMB: Evidence-based medicine, OR 0: oocyte retrieval evening, OR+1/2/3; 1/2/3 day(s) after oocyte retrieval, P: progesterone, IM: intramuscular, SC: subcutaneous, OS: Oral, Vag: vaginal, mg/d: mg per day, PT: pregnancy test; US: ultrasound with detection of hearth activity. EBM data are based on the latest ESHRE guideline on ovarian stimulation 2019".



	Vaginal	IM	Combination	Oral
National Fresh cycle	17.2	9	66.3	1
National Frozen cycle	10.8	9	77.2	3
International Fresh cycle	50	10	30	0
International Frozen cycle	20	20	30	10

Figure 1. **Distribution of route of use of progesterone in national& international clinicians in fresh& frozen cycles.**

After the occurrence of pregnancy, 69% of national specialists continued with progesterone for more than 8 weeks (Q31). This is the same policy in their fresh cycles. International experts used a different policy of continuing LPS beyond 8 weeks only in frozen cycles (50%). About 32% of national and 20% of international participants measure progesterone before ET with no consensus on a threshold or a ceiling (Q36–Q38).

Discussion

Our survey aimed to evaluate the real-life practice regarding LPS among EFRE specialists, experts, and international speakers attending EFRE 2022 in Cairo. Many protocols used in current practice reflect physicians' and patients' preferences. This may be partly due to the weakness of evidence involved in the generation of the available guidelines. Progesterone has been universally adopted for LPS, and now it is routinely prescribed in all ART cycles (13).

The survey showed that most participating specialists based their LPS on evidence and patient preferences rather than evidence alone. This shows the importance of surveys, whether patient or physician-directed.

Individualization of LPS became less popular among physicians compared to the last 10-year follow-up survey (8). This probably reflects the gap in basic and clinical research addressing "LPS success predictors".

In the current survey, only 30% of the respondents individualized the LPS regimens. However, in the 10-year longitudinal survey, 55.4 % of respondents individualized LPS (according to ovarian response, stimulation protocol, age, and BMI) and 42.1 % used fixed protocol for all cases (8). This could be explained by resistance to change practice based on new evidence and it may be less practical to prescribe different treatment regimens for patients in the same center.

It is notable that most of the participating physicians agreed on a progesterone start day in fresh cycles but did not agree on an ending day. In Frozen Cycles, they disagreed on both. In this survey, 71% (105/148) started progesterone on the day of OR, 23.6% (35/148) on the next day after OR, 3.38% (5/148) started on OR+ 2 days and only 2.02% (3/148) started 3 days after OR. In ESHRE guidelines on ovarian stimulation 2019, it is recommended to start LPS from day zero to day 3 from OR (Table 3) (14).

In our survey, it was clear that the trend of use of vaginal progesterone alone is declining and a combination with IM is becoming more accepted reflecting the significance of the findings that were reported by Devine et al.

(15). The 10-year survey reported that the use of IM-P decreased from 13% in 2009 to 4.6% in 2019 (8). The results of the 10-year survey were in accordance with the results of the updated Cochrane meta-analysis of vaginal versus IM-P for LPS in ART, IM-P showed no difference in CPRs, OPRs, miscarriages, and LBRs (6). Moreover, according to the recent ESHRE guidelines, any non-oral route of administration for natural progestogen as an LPS can be used (14). Most of the national participants used combined routes (vaginal and parenteral), as they thought that the vaginal route only may decrease PR. However, in the 10-year survey, only 16% used combinations (8). In another recent survey 2017–2018, they reported that 80% of the clinicians preferred the vaginal route only as LPS, and only 4% used combined vaginal progesterone with intramuscular or oral progesterone which is surprisingly opposite to our results (7). This could be explained by side effects of IM progesterone and patients usually don not prefer parenteral route.

More physicians in this survey are convinced that intramuscular progesterone can be used every three days rather than daily, which is supported by pharmacokinetic studies (16). This shows how a well-designed and published randomized study can change practice very quickly. Although the study published by Devine et al. (15) addressed frozen cycles, physicians applied the conclusion to fresh cycles.

The popularity of incorporating estradiol in LPS protocols is not supported by current evidence. In the Cochrane review for LPS compared progesterone versus a combination of progesterone and estrogen, the results for clinical pregnancy rate in the subgroup of progesterone versus progesterone with transdermal estrogen suggested a significant benefit from combined estrogen progesterone, but there was no difference for other outcomes (6). However, several other studies (17) and ESHRE guidelines were not in agreement (14). It is reasonable to add estradiol to LPS in agonist triggered cycles but the practice of adding it to all cycles may be based on clinical experience but not supported by evidence.

The change of practice, not driven by guidelines, could indicate that either guideline development groups need to be more sensitive to real-life practice involving patient and care provider preferences, or that doctors need to read and apply guidelines more frequently.

In frozen cycles prolonging estradiol treatment for 12 days or more is a practice without strong evidence. Older studies showed that 5–7 days of estrogen is sufficient for endometrial preparation (18, 19). However, others reported a higher miscarriage rate when estrogen priming duration was less than 10 days (20). Longer durations have been also reported by several authors (21, 22). Jiang et al. stated in a retrospective study that the short course of estradiol (7 days) versus conventional (14 days) had no impact on the reproductive outcomes in FET (23).

For monitoring of serum progesterone before ET, 40% of national participants versus only 27% of the international counterparts measured progesterone with no consensus on a threshold or a ceiling. Yovich et al. stated in a large retrospective study of 529 cycles that monitoring serum progesterone in HRT-cryopreserved embryo transfer is necessary and serum progesterone concentrations below 50 nmol/l and above 99 nmol/L were associated with decreased implantation rates (24). A meta-analysis by Melo et al. evaluated 21 studies that measured serum progesterone around the time of FET and concluded that the minimum clinically important serum luteal progesterone level that is associated with optimal ongoing pregnancy or live birth rates is approximately 10 ng/mL (25). In our survey, the majority of national participants do not measure serum progesterone before ET as they already use high dose of LPS.

Strengths and Limitations

First, not all the respondents answered all the questions of the survey. The international participants who do not use IM-P or oral dydrogesterone did not answer these questions, another question like use of SC progesterone so we could not know if they did not answer as they do not use or not. Second, the low response rate, despite being distributed among large sector of IVF practitioners in Egypt but this might be due to online nature of the survey, and this is considered one of the main disadvantages.

Third, the small number of international participants made the comparison not accepted statistically. Forth, there was a lack of national guidelines to standardize the practice. However, this survey has highlighted the gap between evidence and practice. Second, it gave ideas for further research in LPS. Third, some participants started to change their practice after discussion of the results, e.g., IM-p every three days instead of daily dosage which is considered as main advantage and initial step to adhere to guidelines. So, this survey may be considered as the first step to set the framework for national guidelines aiming to standardize the practice.

Conclusion

In conclusion, the current survey underscores the importance of evaluating real-life practice in LPS protocols. It highlights gaps in knowledge and clinical practice, suggesting a more controlled guideline-driven practice, and invites the design of robust RCT addressing areas of controversy.

There is a reasonable area of consensus among practitioners in the field of LPS in ART. There is a variation in modes of delivery of progesterone, doses, and schedule among participants. The practice is not individualized and not specifically adherent to guidelines in the P dose, formulation and when to stop LPS. The reason why previous surveys are not involved in decision-making is not quite clear.

Declarations

Ethical Approval and consent to participate;

Not applicable, Institutional review board approval was not required for this survey as it did not contain patients' data.

Consent for publication; Approved from Ethics committee, Faculty of Medicine, Alexandria University.

Availability of data and material; the datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests; the authors declare that they have no competing interests.

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