\$ sciendo

ACTA MEDICA TRANSILVANICA March 26(1):59-62 DOI: 10.2478/amtsb-2020-0016 Online ISSN 2285-7079

THE EFFECTIVENESS OF PROGESTINS FOR PITUITARY SUPPRESSION DURING OVARIAN STIMULATION IN IVF PROCEDURES

ALEXANDRU POLEXA¹, SULE YILDIZ², BARIS ATA³

¹ "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu-Mureş, ^{1,2,3}Koc University Hospital, Istanbul, Turkey

Keywords: progestins, Ovarian stimulation, IVF Abstract: Progestins are capable of suppressing endogenous luteinizing hormone (LH) secretion from the pituitary; are less expensive than GnRH analogues. This systematic review summarizes the effectiveness of progestins as compared with GnRH analogues and identifies some of the future research perspectives. Several public resources were screened with a combination of keywords related to assisted reproductive technology, progesterone, GnRH analogue and ovarian stimulation. Overall, duration of stimulation, gonadotropin consumption and oocyte yield were similar with progestins and GnRH analogues. The live birth, ongoing and clinical pregnancy rates per embryo transfer were similar with progestins and GnRH analogues. There is still a low quality of evidence. Available information is reassuring regarding obstetric and neonatal outcomes with the use of progestins. As a wider implication, progestins can present an effective option for women who do not contemplate a fresh embryo transfer, anticipated hyper responders, preimplantation genetic testing, oocyte donors, double stimulation cycles.

INTRODUCTION

Pituitary suppression is commonly achieved by gonadotropin releasing hormone (GnRH) analogues. GnRH antagonists have become the most commonly used agents for over a decade, since they require less injections, provide similar pregnancy rates and lower risk of ovarian hyperstimulation syndrome than the former standard of care, i.e. GnRH agonists.(1) Progestins are also capable of suppressing endogenous luteinizing hormone (LH) secretion from the pituitary.(2) Unlike GnRH analogues, progestins can be used orally and cost significantly less than GnRH antagonists. However, early endometrial exposure to progestin precludes a fresh embryo transfer.(3) Yet, with the advent of high-survival embryo vitrification and increasing number of oocyte cryopreservation cycles progestins are being more frequently used in ART. However, there is limited information about the effectiveness of progestins as compared with GnRH analogues.

AIM

This systematic review summarizes the effectiveness of progestins as compared with GnRH analogues and identifies some of the future research perspectives.

MATERIALS AND METHODS

Briefly, we searched Cochrane Central Register of Controlled Trials (CENTRAL); Medline via PubMed; Web of Science; Scopus and manually screened the reference lists of selected articles. Search period was from the date of inception of each database until 1 April 2020. There were included all studies that compared the effectiveness of a progestin with GnRH analogue for pituitary suppression in ART, which were published as full text in English. The primary outcome was *live birth* of a fetus after 20 completed weeks of gestational age per woman starting a stimulation cycle. Secondary outcomes were i) *live birth or ongoing pregnancy* beyond 12 weeks *per woman* starting a stimulation cycle, ii) *live birth rate per embryo transfer procedure, iii) live birth or ongoing pregnancy per embryo transfer procedure,* iv) *clinical pregnancy* (defined as evidence of a gestational sac at six weeks or later, confirmed with ultrasound) *rate per embryo transfer procedure,* v) *number of oocytes retrieved per OR, vi) number of metaphase two oocytes per OR,* vii) the duration of a stimulation cycle, viii) total gonadotropin consumption per stimulation cycle.

Adverse events included; i) ectopic pregnancy per embryo transfer, ii) miscarriage per pregnancy: defined as the number of spontaneous abortions (pregnancy loss before 20 completed weeks of gestation) and the number of stillbirths (pregnancy loss after 20 completed weeks of gestation), *iii*) multiple pregnancy rate per embryo transfer and iv) ovarian hyperstimulation syndrome (OHSS) per stimulation cycle.

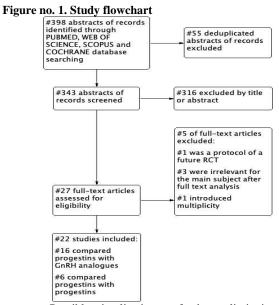
RESULTS

We included 10 studies comparing progestins with GnRH antagonists, six with GnRH agonists (one of which was treated as two separate studies since there were two distinct study populations involved, Shen et al. 2020) (4), and six with other progestins or different dosages of the same progestin (figure no. 1).

There are several important limitations of the available studies; i) majority of them were conducted in the same center by the two groups of investigators from China, ii) in most studies patients were allocated to different protocols in a nonrandomized manner, iii) pregnancy outcomes were reported per transfer rather than per woman starting stimulation. Moreover, cumulative live birth rates per stimulation, which is the most relevant outcome measure was not reported at all.

¹Corresponding author: Alexandru Polexa, Str. Ștefan cel Mare, Nr. 2, Bl. 10, Sc. B, Ap. 11, Brașov, România, E-mail: polexa_a@yahoo.com, Phone: +40744 125195

Article received on 02.11.2020 and accepted for publication on 26.02.2021



Possible implications of these limitations vary depending on the outcome of interest. In order to address these shortcomings, it can be useful to separate outcomes in two categories; the first category includes outcomes related to the response to ovarian stimulation (ROS), i.e. duration of stimulation, total gonadotropin consumption, number of oocytes and mature oocytes collected, risk of OHSS, while the second category includes outcomes after embryo transfer (ET), i.e. pregnancy, multiple pregnancy, miscarriage and live birth rates. We are presenting as numeric data the ET outcomes for the both GnRH antagonists and agonists. The outcomes in ROS category were reported per woman starting stimulation cycle and the major risk is selection bias in the non-randomized studies. Despite similar baseline characteristics regarding age and ovarian reserve parameters being reported for study groups in all papers, it is impossible to completely rule out systematic differences in other parameters that can probably effect ovarian response between the groups, e.g. the selection of starting gonadotropin dosage, which would have an impact on total gonadotropin consumption and could have been effected by the knowledge of pituitary suppression protocol planned for a patient, or monitoring could have been done differently. Yet, we think outcomes in this category are more reliable than outcomes in the ET category. The latter is crippled by the failure to report pregnancy/live birth rates per woman starting stimulation and cannot account for women not reaching an embryo transfer or women undergoing multiple embryo transfers. The proportion of women undergoing ET over women starting stimulation ranged between 25 - 91% in PPOS arms and 50 - 88% in comparators and were significantly different between PPOS and GnRH analogue groups in some studies (data not shown). Moreover, observations in ROS category can have higher generalizability than the observations in ET category. The data is dominated by studies on Chinese women, while ethnic differences may arguably have an effect on pregnancy and live birth rates, ovarian response does not seem to be effected by ethnic background based on limited data.(5,6,7)

Progestins versus GnRH Antagonists

Progestins were compared with GnRH antagonists in ten studies. Three were RCTs (8,9,10) two were prospective (11,12) and five were retrospective cohort studies.(13,14,15,16,17) Regarding ET outcomes, only one study reported live birth rate per woman starting stimulation.(9) There were 170 women in each group and women in the PPOS and GnRH antagonist groups had similar live birth rates (21.8% vs 18.2%, respectively, p=0.42) However, in addition to the lack of allocation concealment, it is unclear whether women underwent multiple embryo transfers, i.e. fresh followed by frozen transfers if the fresh transfer did not result in live birth. Moreover, the trial was underpowered for comparison of live birth rates (figure no. 2).

Figure no. 2. Progestins versus GnRH Antagonists – Embryo transfer outcomes

Study or Subgroup		Total	GnRH Antago Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
2.2.1 Live Birth Rate	10 H H H H		263	20235	1000		
Chen 2019 Subtotal (95% CI)	37	170 170	31	170 170	3.7% 3.7%	1.19 [0.78, 1.83] 1.19 [0.78, 1.83]	
Total events	37		31				1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Heterogeneity: Not a Test for overall effect		(P = 0	.42)				
2.2.2 Live Birth Rate Chen 2019	e per Embry 37	122	nster 31	116	4.0%	1.13 [0.76, 1.70]	
Huang P 2019	16	50	20	112	2.3%	1.79 [1.02, 3.16]	
Subtotal (95% CI)		172		228	6.4%	1.36 [0.88, 2.11]	
Total events	53		51	A 300.			
Heterogeneity: Tau ² Test for overall effect				0.20);	r = 40%		
2.2.3 Live Birth or O	Ingoing Pre	egnan	cy Rate per Em	bryo Tr	ansfer		
Chen 2019	37	122	31	116	4.0%	1.13 [0.76, 1.70]	
Huang P 2019	16	50	20	112	2.3%	1.79 [1.02, 3.16]	
wami 2018 Xiao 2019	78 28	195	77 33	202	7.5%	1.05 [0.82, 1.34]	
Subtotal (95% CI)	40	53 420	33	504	4.67	1.16 [0.83, 1.70] 1.15 [0.97, 1.37]	
Total events	159		161				
Heterogeneity: Tau ² Test for overall effect				0.40);	ř = 0%		
2.2.4 Live Birth or O	ngoing Pre	egnan	cy Rate per Em	bryo Tr	ansfer in	Oocyte Recipients	
Begueria 2019	31	153	42	155	4.0%	0.75 [0.50, 1.12]	
Yikitz 2019 Subtotal (95% CI)	43	86	51	105	6.3%	1.03 [0.77, 1.37]	
Subtotal (95% CI) Total events	74	239	93	260	10.3%	0.91 [0.66, 1.24]	-
Heterogeneity: Tau ²		² =1		0.20):	r ² = 39%		
Test for overall effect				1			
2.2.5 Clinical Pregna							
Chen 2019	48	122	39	116	5.2%	1.17 [0.84, 1.64]	
Eftekhar 2019	6	41	15	51	1.1%	0.50 [0.21, 1.17]	
Huang P 2019 Iwami 2018	19 103	50 195	25 100	112 202	2.9%	1.70 [1.04, 2.79] 1.07 [0.88, 1.29]	
Xiao 2019	30	53	38	74	5.5%	1.10 [0.80, 1.52]	
Subtotal (95% CI)	5022	461		555	24.1%	1.12 [0.91, 1.38]	•
Total events	206		217				
Heterogeneity: Tau ² Test for overall effect				0.16);	r = 39%		
2.2.6 Clinical Pregna	ancy per Er	nbryo	Transfer in Oo	ocyte Re	cipients		
Begueria 2019	47	153	71	155	6.2%	0.67 [0.50, 0.90]	
Martinez 2019	101	154	88	146	10.1%	1.09 [0.91, 1.30]	
Yikitz 2019 Subtotal (95% CI)	55	86 393	66	105 406	8.5% 24.8%	1.02 [0.82, 1.26] 0.93 [0.71, 1.21]	
Total events	203		225	400	1.0/4	0.55 [0.74, 1.14]	
Heterogeneity: Tau ²	= 0.04; Chi		42, df = 2 (P =	0.01);	r ² = 76%		
Test for overall effect	t: Z = 0.57	(P = 0	.57)				
2.2.7 Miscarriage Ra	10.200						
Chen 2019	9	48	8	39	1.1%	0.91 [0.39, 2.15]	
Eftekhar 2019 Huang P 2019	8 3	13 19	9	24 25	1.7%	1.64 [0.84, 3.21] 0.79 [0.21, 2.90]	
Iwami 2018	25	103	23	100	2.9%	1.06 [0.64, 1.73]	
Xiao 2019	2	30	4	38	0.3%	0.63 [0.12, 3.23]	
Subtotal (95% CI)	18 (52)	213	122	226	6.6%	1.11 [0.79, 1.56]	•
Total events Heterogeneity: Tau ²				0.67);	r² = 0%		
Test for overall effect							
2.2.8 Multiple Pregn			a a su a				
Chen 2019 Wami 2018	12	122	3	116 202	0.6%	3.60 [1.10, 13.13] 1.55 [0.26, 9.20]	
Xiao 2019	7	53	9	74	1.0%	1.09 [0.43, 2.73]	
Subtotal (95% CI)		370		392	1.8%	1.74 [0.78, 3.92]	
Total events Heterogeneity: Tau ² Test for overall effect				0.27);	r² = 23%		
2.2.9 Multiple Pregn	nancy per V	Vomar	Undergoing E	mbryo	Transfer	in Oocyte Recipients	
Begueria 2019	13	153	6	155	0.9%	2.19 [0.86, 5.63]	
Yikitz 2019	18	86	26	105	2.6%	0.85 [0.50, 1.43]	
Subtotal (95% CI) Total support		239		260	3.6%	1.26 [0.50, 3.18]	
Total events Heterogeneity: Tau ²				0.08);	r ² = 67%		
Test for overall effect	c Z = 0.48	() = (.03)				
							0.1 0.2 0.5 1 2 5
							More in GnRH Antagonists More in Progestins

Progestins vs GnRH agonists

Progestins were compared with GnRH agonists in six

AMT, vol. 26, no. 1, 2021, p. 60

studies. Two were RCTs, one prospective and three were retrospective cohort studies.(4,18,19,20,21,22) One of the RCTs was indeed a quasi-randomized trial and assignment was by patient numbers, which clearly breaches the principle of allocation concealment.(19) All studies were from the Dept. of Assisted Reproduction of Shangai Ninth People's Hospital and included women with an anticipated normal ROS or PCOS.

Figure no. 3. Progestins	versus GnRH	Agonists –	Embryo
transfer outcomes			

tudy or Subgroup		tins	GnRH Antag	onists		Risk Ratio	Risk Ratio
		Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.1 Live Birth Rat	10.2		288	12230	2000		
hen 2019	37	170	31	170	3.7%	1.19 [0.78, 1.83]	
ubtotal (95% CI)	47	170		170	3.7%	1.19 [0.78, 1.83]	-
otal events eterogeneity: Not a	37 Indicable		31				
est for overall effect		(P = 0.	42)				
.2.2 Live Birth Rat	e per Embr	yo Tran	sfer				
hen 2019	37	122	31	116	4.0%	1.13 [0.76, 1.70]	
uang P 2019	16	50	20	112	2.3%	1.79 [1.02, 3.16]	
ubtotal (95% CI)		172		228	6.4%	1.36 [0.88, 2.11]	
otal events eterogeneity: Tau ² est for overall effec				= 0.20);	i ² = 40%		
.2.3 Live Birth or (Ongoing Pr	egnanc	y Rate per Er	nbryo Tr	ansfer		
hen 2019	37	122	31	116	4.0%	1.13 [0.76, 1.70]	
uang P 2019	16	50	20	112	2.3%	1.79 [1.02, 3.16]	
vami 2018	78	195	77	202	7.5%	1.05 [0.82, 1.34]	
lao 2019	28	53	33	74	4.8%	1.18 [0.83, 1.70]	
ubtotal (95% CI)	104	420	101	504	18.7%	1.15 [0.97, 1.37]	•
otal events eterogeneity: Tau ²	159 - 0.00- CH	×- 20	161 2 df = 3/P	- 0 40)-	P _ AV		
est for overall effect				- 0.40/,	- 1/4		
.2.4 Live Birth or (Ongoing Pr	egnanc	y Rate per Er	nbryo Tr	ansfer in	Oocyte Recipients	
egueria 2019	31	153	42	155	4.0%	0.75 [0.50, 1.12]	
lidiz 2019	43	86	51	105	6.3%	1.03 [0.77, 1.37]	+
ubtotal (95% CI)		239	5533 4240	260	10.3%	0.91 [0.66, 1.24]	+
otal events eterogeneity: Tau ²				= 0.20);	r ² = 39%		
est for overall effec	t: Z = 0.62	(P = 0.	54)				
.2.5 Clinical Pregn	ancy per Er		Fransfer				
hen 2019	48	122	39	116	5.2%	1.17 [0.84, 1.64]	
ftekhar 2019	6	41	15	51	1.1%	0.50 [0.21, 1.17]	· · · · · · · · ·
uang P 2019	19	50	25	112	2.9%	1.70 [1.04, 2.79]	10 10 10 10 10 10 10 10 10 10 10 10 10 1
wami 2018	103	195	100	202	9.4%	1.07 [0.88, 1.29]	
lao 2019 ubtotal (95% CI)	30	53 461	38	74 555	5.5% 24.1%	1.10 [0.80, 1.52] 1.12 [0.91, 1.38]	-
otal events	206		217	333	- 114/6	**** [0:54] 1:30]	
eterogeneity: Tau ² est for overall effec	= 0.02; Ch		3, df = 4 (P +	= 0.16);	i ² = 39%		
eterogeneity: Tau ²	= 0.02; Ch t: Z = 1.09	(P = 0.	3, df = 4 (P + 28)				
eterogeneity: Tau ² est for overall effec .2.6 Clinical Pregn egueria 2019	= 0.02; Ch t: Z = 1.09 hancy per Er 47	(P = 0. mbryo 1 153	3, df = 4 (P + 28) Fransfer in O 71	ocyte Re 155	cipients 6.2%	0.67 [0.50, 0.90]	
eterogeneity: Tau ² est for overall effec .2.6 Clinical Pregn eguerta 2019 lartínez 2019	= 0.02; Ch at: Z = 1.09 ancy per Er 47 101	(P = 0. mbryo 1 153 154	3, df = 4 (P + 28) Fransfer in O 71 88	ocyte Re 155 146	cipients 6.2% 10.1%	1.09 [0.91, 1.30]	
eterogeneity: Tau ² est for overall effec .2.6 Clinical Pregn egueria 2019 lartínez 2019 lidiz 2019	= 0.02; Ch t: Z = 1.09 hancy per Er 47	(P = 0. mbryo 1 153 154 86	3, df = 4 (P + 28) Fransfer in O 71	ocyte Re 155 146 105	cipients 6.2% 10.1% 8.5%	1.09 [0.91, 1.30] 1.02 [0.82, 1.26]	-
eterogeneity: Tau ² est for overall effec .2.6 Clinical Pregn egueria 2019 lartínez 2019 lidiz 2019 ubtotal (95% CI)	= 0.02; Ch at: Z = 1.09 ancy per Er 47 101 55	(P = 0. mbryo 1 153 154	3, df = 4 (P + 28) Transfer in O 71 88 66	ocyte Re 155 146	cipients 6.2% 10.1%	1.09 [0.91, 1.30]	
eterogeneity: Tau ² est for overall effec .2.6 Clinical Pregn egueria 2019 lartínez 2019 lidiz 2019	= 0.02; Ch ancy per Er 47 101 55 203 = 0.04; Ch	(P = 0. mbryo 1 153 154 86 393 F = 8.4	3, df = 4 (P 28) Fransfer in O 71 88 66 225 2, df = 2 (P	locyte Re 155 146 105 406	cipients 6.2% 10.1% 8.5% 24.8%	1.09 [0.91, 1.30] 1.02 [0.82, 1.26]	
eterogeneity: Tau ² est for overall effec 2.6 Clinical Pregn egueria 2019 lartinez 2019 lidiz 2019 ubtotal (95% Cl) otal events eterogeneity: Tau ² est for overall effec 2.7 Miscarriage R	= 0.02; Ch t; Z = 1.09 ancy per Er 47 101 55 203 = 0.04; Ch t; Z = 0.57 ate per Pres	(P = 0. 153 154 86 393 I ² = 8.4 (P = 0. gnancy	3, df = 4 (P + 28) Fransfer in O 71 88 66 225 2, df = 2 (P + 57)	ocyte Re 155 146 105 406 = 0.01);	cipients 6.2% 10.1% 8.5% 24.8% F = 76%	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21)	
eterogeneity: Tau ² est for overall effec 2.6 Clinical Pregn egueria 2019 fartinez 2019 lidiz 2019 ubtotal (95% Cl) otal events eterogeneity: Tau ² est for overall effec 2.7 Miscarriage R hen 2019	= 0.02; Ch t; Z = 1.09 ancy per Er 47 101 55 203 = 0.04; Ch t; Z = 0.57 ate per Pres 9	(P = 0. mbryo 1 153 154 86 393 I ² = 8.4 (P = 0. gnancy 48	3, df = 4 (P + 28) Fransfer in O 71 88 66 225 2, df = 2 (P + 57) 8	locyte Re 155 146 105 406 = 0.01); 39	cipients 6.2% 10.1% 8.5% 24.8% F = 76% 1.1%	1.09 [0.91, 1.30] 1.02 [0.82, 1.26] 0.93 [0.71, 1.21] 0.91 [0.39, 2.15]	
eterogeneity: Tau ² est for overall effec 2.6 Clinical Pregn gyueria 2019 latrinez 2019 lidiz 2019 ubtotal (95% Cl) otal events eterogeneity: Tau ² est for overall effec 2.7 Miscarriage R hen 2019 ftekhar 2019	= 0.02; Ch ancy per En- 47 101 55 203 = 0.04; Ch at per Prey 9 8	(P = 0. mbryo 1 153 154 86 393 f ² = 8.4 (P = 0. gnancy 48 13	3, df = 4 (P + 28) 71 88 66 225 2, df = 2 (P + 57) 8 9	locyte Re 155 146 105 406 = 0.01); 39 24	cipients 6.2% 10.1% 8.5% 24.8% F = 76% 1.1% 1.7%	1.09 [0.91, 1.30] 1.02 [0.82, 1.26] 0.93 [0.71, 1.21] 0.91 [0.39, 2.15] 1.64 [0.84, 3.21]	•
eterogeneity: Tau ² est for overall effec est for overall effec egueria 2019 latricez 2019 lidiz 2019 luidiz 2019 luidiz 405% CI) otal events eterogeneity: Tau ² est for overall effec a.2.7 Miscarriage R hen 2019 ftekhar 2019	= 0.02; Ch ancy per En- 47 101 55 203 = 0.04; Ch at per Prey 9 8 3	(P = 0. 153 154 86 393 P = 8.4 (P = 0. gnancy 48 13 19	3, df = 4 (P + 28) 71 88 66 225 2, df = 2 (P + 57) 8 9 5	ocyte Re 155 146 105 406 = 0.01); 39 24 25	cipients 6.2% 10.1% 8.5% 24.8% P = 76% 1.1% 1.7% 0.5%	1.09 [0.91, 1.30] 1.02 [0.82, 1.26] 0.93 [0.71, 1.21] 0.91 [0.39, 2.15] 1.64 [0.84, 3.21] 0.79 [0.21, 2.90]	
eterogeneity: Tau ² est for overall effec 2.6 Clinical Pregn egueria 2019 lartinez 2019 lidiz 2019 lidiz 2019 est for overall effec 2.7 Miscarriage R hen 2019 frehar 2019 nami 2019 nami 2018	= 0.02; Ch at Z = 1.09 47 101 55 203 = 0.04; Ch at Z = 0.57 ate per Prey 8 3 25	(P = 0. mbryo 1 153 154 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103	3, df = 4 (P + 28) Fransfer in O 71 88 66 225 2, df = 2 (P + 57) 8 9 5 23	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100	cipients 6.2% 10.1% 8.5% 24.8% F = 76% 1.1% 1.7% 0.5% 2.9%	1.09 [0.91, 1.30] 1.02 [0.82, 1.26] 0.93 [0.71, 1.21] 0.91 [0.39, 2.15] 1.64 [0.84, 3.21] 0.79 [0.21, 2.90] 1.06 [0.64, 1.73]	
eterogeneity: Tau ² est for overall effect 2.6 Clinical Pregn gueria 2019 ditiz 2019 ditiz 2019 ubtotal (95% CI) otal events eterogeneity: Tau ² eterogeneity: Tau ² eterogene	= 0.02; Ch ancy per En- 47 101 55 203 = 0.04; Ch at per Prey 9 8 3	(P = 0. mbryo 1 153 154 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103 30	3, df = 4 (P + 28) 71 88 66 225 2, df = 2 (P + 57) 8 9 5	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38	cipients 6.2% 10.1% 8.5% 24.8% F = 76% 1.1% 1.7% 0.5% 2.9% 0.3%	1.09 [0.91, 1.30] 1.02 [0.82, 1.26] 0.93 [0.71, 1.21] 0.91 [0.39, 2.15] 1.64 [0.84, 3.21] 0.79 [0.21, 2.90] 1.66 [0.64, 1.73] 0.63 [0.12, 3.23]	
eterogenehy-Tau ² est for overall effect 2.6 Clinical Pregne gueria 2019 lartinez 2019 lartinez 2019 laftez 2019 ubtotal (95% Cl) otal events est for overall effect 2.7 Miscarriage R hen 2019 hethar 2019 nami 2018 hang 2019 ubtotal (95% Cl) otal events	= 0.02; Ch t; Z = 1.09 hancy per Er 47 101 55 203 = 0.04; Ch t; Z = 0.57 ate per Prey 8 3 25 2 47 47 47 47 47 101 55 203 47 47 101 55 203 47 203 203 25 2 47 47 47 101 55 203 47 203 203 203 205 205 205 205 205 205 205 205	(P = 0. 153 154 86 393 P ² = 8.4 (P = 0. gnancy 48 13 19 103 30 213	3, df = 4 (P - 28) Fransfer in O 71 88 66 225 2, df = 2 (P - 57) 8 9 5 23 4 4 9	155 146 105 406 = 0.01); 39 24 25 100 38 226	scipients 6.2N 10.1N 8.5N 24.8% ₽ = 76N 1.1N 1.7N 0.5N 2.9N 0.3N 6.6%	1.09 [0.91, 1.30] 1.02 [0.82, 1.26] 0.93 [0.71, 1.21] 0.91 [0.39, 2.15] 1.64 [0.84, 3.21] 0.79 [0.21, 2.90] 1.06 [0.64, 1.73]	
eterogenehy-Tau ² est for overall effec 2.6 Clinical Pregne egueria 2019 latrinez 2019 lidic 2019 ubtotal (95% Cl) otal events eterogenehy-Tau ² eterogenehy-Tau ²	= 0.02; Ch t: Z = 1.09 kancy per Er 101 55 203 = 0.04; Ch t: Z = 0.57 ate per Pres 8 3 25 2 47 = 0.00; Ch	(P = 0. 153 154 86 87 87 87 87 87 87 87 87 87 87	3, df = 4 (P - 28) Fransfer in O 71 88 66 225 2, df = 2 (P - 57) 8 9 5 23 4 49 5, df = 4 (P -	155 146 105 406 = 0.01); 39 24 25 100 38 226	scipients 6.2N 10.1N 8.5N 24.8% ₽ = 76N 1.1N 1.7N 0.5N 2.9N 0.3N 6.6%	1.09 [0.91, 1.30] 1.02 [0.82, 1.26] 0.93 [0.71, 1.21] 0.91 [0.39, 2.15] 1.64 [0.84, 3.21] 0.79 [0.21, 2.90] 1.66 [0.64, 1.73] 0.63 [0.12, 3.23]	
eterogenehy: Tau ¹ est for overall effect 2.6 Clinical Pregn gueria 2019 utinte: 2019 utinte: 2019 ubtotal (95% Cl) otal events eterogenehy: Tau ¹ eter for overall effect 2.7 Miscarriage R hen 2019 ump 2019 ump 2019 ump 2019 ubtotal (95% Cl) otal events eterogenehy: Tau ¹ est for overall effect 2.8 Multiple Preg. 2.8 Multiple Preg.	= 0.02; Ch U = 1.09 ancy per Er 47 101 55 203 = 0.04; Ch U = 0.57 20 203 204; Ch U = 0.57 203 205 2 2 4 7 4 7 5 5 2 4 7 4 7 5 5 8 8 8 3 2 5 5 2 4 7 4 7 7 7 8 8 8 8 8 8 9 8 8 8 8 9 8 8 8 8 9 8 8 8 8 9 8 9 8 8 8 8 9 8 8 8 9 8 8 8 9 8 8 8 8 9 8 8 8 9 8 8 8 9 8 8 8 9 8 8 8 9 8 8 8 9 8 8 8 9 8 8 8 9 8 8 8 9 8 8 8 9 8 8 8 9 8 8 9 8 8 8 8 9 8 8 8 9 8 8 8 8 8 9 8 8 8 8 9 8 8 8 8 9 8 8 8 8 8 8 8 9 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	(P = 0. mbryo 1 153 154 86 393 P ² = 8.4 (P = 0. gnancy 48 13 19 103 30 213 P ² = 2.3 (P = 0. Voman	3, df = 4 (P + 28) Fransfer in Q 71 88 66 225 2, df = 2 (P + 57) 8 9 5 23 4 49 5, df = 4 (P - 56) Undergoing	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 226 ; ; Embryo	ccipients 6.2% 8.5% 24.8% 1.1% 24.8% 1.1% 1.7% 0.5% 2.9% 0.3% 6.6% 1* = 0%	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 1.64 (0.84, 3.21) 0.79 (0.21, 2.90) 1.66 (0.34, 3.21) 0.63 (0.12, 3.23) 1.11 (0.79, 1.36)	
eterogenehy: Tau ¹ est for overall effect 2.6 Clinical Pregn gueria 2019 utilize 2019 lidiz 2019 lidiz 2019 lidiz 2019 lidiz 2019 lidiz 2019 et overall effect 2.7 Miscarriage R fen 2019 findar 2019 lidiz 2019	= 0.02; ChA22 - 1.09 ancy per Er 47 47 - 101 55 500 500 - 100 8 9 8 8 3 25 2 2 47 7 = 0.00; ChA22 - 0.59 8 8 3 25 2 47 7 = 0.00; ChA22 - 0.59 9 8 8 3 25 2 47 7 10 10 10 10 10 10 10 10 10 10 10 10 10	(P = 0. mbryo 1 153 154 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103 30 213 P = 2.3 (P = 0. Voman 122	3, df = 4 (P + 26) Fransfer in O 71 88 66 225 2, df = 2 (P + 57) 8 9 5 23 4 49 5, df = 4 (P + 56) Undergoing 3	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 226 = 0.67); Embryo 116	6.2% 6.2% 10.1% 8.5% 24.8% 24.8% 24.8% 1.1% 1.7% 0.5% 0.5% 0.5% 0.5% 0.5% 2.9% 0.3% 6.6%	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.91 (0.39, 2.15) 1.64 (0.84, 3.12) 0.79 (0.21, 2.80) 1.06 (0.64, 1.73) 0.63 (0.12, 3.23) 1.11 (0.79, 1.56) 3.60 (1.10, 13.13)	
eterogeneity: Tau ² est for overal effect 2.6 Clinical Pregn egueta 2019 attinez 2019 ubtotal (95% Cl) otal events eterogeneity: Tau ² est for overall effect 2.7 Miscarriage R herbar 2019 herbar 2	= 0.02; ChA22 - 1.09 ancy per Er 47 - 1.09 203 - 204; ChA22 - 204; ChA22 - 204; ChA22 - 204; ChA22 - 204; ChA22 - 204; ChA22 - 204; ChA	(P = 0. mbryo 1 153 154 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103 30 213 P = 2.3 (P = 0. Voman 122 195	3, df = 4 (P · 4 28) Fransfer in O 225 2, df = 2 (P · 1 8 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 7 1 Underson (Contention of the content of the c	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 = 0.67); Embryo 116 202	ccipients 6.2% 8.5% 8.5% 24.8% ₽ = 76% 1.1% 1.7% 0.5% 0.3% 6.6% ₽ = 0% Transfer 0.6% 0.3%	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 1.64 (0.84, 3.21) 0.95 (0.21, 2.90) 1.66 (0.64, 1.73) 0.63 (0.12, 3.23) 1.11 (0.79, 1.56) 3.80 (1.10, 13.13) 1.55 (0.26, 9.20)	
eterogenehy: Tau ¹ est for overall effect 2.6 Clinical Pregn gueria 2019 artinez 2019 libit 2019 libit 2019 libit 2019 libit 2019 libit 2019 ett for overall effect 2.7 Miscarriage R hen 2019 ann 2 2018 lib 2 2019	= 0.02; ChA22 - 1.09 ancy per Er 47 47 - 101 55 500 500 - 100 8 9 8 8 3 25 2 2 47 7 = 0.00; ChA22 - 0.59 8 8 3 25 2 47 7 = 0.00; ChA22 - 0.59 9 8 8 3 25 2 47 7 10 10 10 10 10 10 10 10 10 10 10 10 10	(P = 0. mbryo 1 153 154 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103 30 213 P = 2.3 (P = 0. Voman 122 135 53	3, df = 4 (P + 26) Fransfer in O 71 88 66 225 2, df = 2 (P + 57) 8 9 5 23 4 49 5, df = 4 (P + 56) Undergoing 3	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 = 0.67); 16 202 202 74	6.2× 10.1× 8.5× 24.8× 1.1× 1.7× 0.5× 2.9× 0.3× 6.6× 7 = 0× Transfer 0.6× 1.0×	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.91 (0.39, 2.15) 1.64 (0.84, 3.21) 0.79 (0.21, 2.90) 1.69 (0.43, 2.33) 1.11 (0.79, 1.36) 3.80 (1.10, 1.3.13) 1.55 (0.26, 9.20) 1.69 (0.43, 2.73)	
eterogenehy: Tau ¹ est for overall effect 2.6 Clinical Pregn gueria 2019 artinez 2019 lidiz 2019 lidiz 2019 lidiz 2019 lidiz 2019 lidiz 2019 lidiz 2019 eterogenehy: Tau ¹ est for overall effect 2.7 Miscarriage R feata 2019 fieldar 2019 mani 2018 lidiz 2019 lidiz 2018 lidiz 2018 lidiz 2018 lidiz 2018 lidiz 2018 lidiz 2018 lidiz 2018	= 0.02; Ch 02; C	(P = 0. mbryo 1 153 154 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103 30 213 P = 2.3 (P = 0. Voman 122 195	3, df = 4 (P + 28) Transfer in O 71 88 86 86 225 2, df = 2 (P + 2 9 5, df = 2 (P + 2 4 4 5, df = 4 (P + 56) 10 10 10 10 10 10 10 10 10 10	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 = 0.67); Embryo 116 202	ccipients 6.2% 8.5% 8.5% 24.8% ₽ = 76% 1.1% 1.7% 0.5% 0.3% 6.6% ₽ = 0% Transfer 0.6% 0.3%	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 1.64 (0.84, 3.21) 0.95 (0.21, 2.90) 1.66 (0.64, 1.73) 0.63 (0.12, 3.23) 1.11 (0.79, 1.56) 3.80 (1.10, 13.13) 1.55 (0.26, 9.20)	
eterogenehy: Tau ¹ est for overall effect 2.6 Clinical Pregn gueria 2019 artinez 2019 libit 2019 libit 2019 libit 2019 libit 2019 libit 2019 ett for overall effect 2.7 Miscarriage R hen 2019 ann 2 2018 lib 2 2019	= 0.02; Ch U = 0.0	(P = 0. mbryo 1 153 154 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103 30 213 P = 2.3 (P = 0. Woman 122 195 53 370 P = 2.6	3, df - 4 (P - 28) Transfer in O 71 88 66 225 2, df - 2 (P - 55 55 55 55 56) Undergoing 3 2 9 14 4, df - 2 (P -	ocyte Re 155 146 406 406 406 406 406 406 406 4	scipients 6.2% 10.1% 8.5% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8%24% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8% 24.8%24% 24.8% 24.8%24% 24.8% 24.8% 24.8%24% 24.8% 24.8% 24.8%24% 24.8% 24.8%24% 24.8% 24.8%24% 24.8% 24.8%24% 24.8% 24.8%24% 24.8%24% 24.8% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24.8%24% 24% 24%24% 24% 2%24% 24% 24%24% 24% 24%24% 24% 24%24% 24% 24%24% 24% 24% 24%24% 24% 24%24% 24% 24%24% 24% 24%24% 24% 24%24% 24%	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.91 (0.39, 2.15) 1.64 (0.84, 3.21) 0.79 (0.21, 2.90) 1.69 (0.43, 2.33) 1.11 (0.79, 1.36) 3.80 (1.10, 1.3.13) 1.55 (0.26, 9.20) 1.69 (0.43, 2.73)	
eterogenehy: Tau ² est for overall effect 2.6 Clinical Pregn egueta 2019 attrinez 2019 ubtotal (95% Cl) otal eents eterogenehy: Tau ² est for overall effect est for overall effect 2.7 Miscarriage R hen 2019 umor 2019 ubtotal (95% Cl) otal eents eterogenehy: Tau ² est for overall effect 2.8 Multiple Preg hen 2019 ubtotal (95% Cl) otal events eterogenehy: Tau ² est for overall effect 2.8 Multiple Preg len 2019 ubtotal (95% Cl) otal events eterogenehy: Tau ² est for overall effect	= 0.02; Ch H tr Z = 1.09 47 101 55 203 = 0.04; Ch tr Z = 0.57 2 2 47 = 0.00; Ch tr Z = 0.59 7 = 0.00; Ch tr Z = 0.59 7 2 2 3 7 2 2 - 0.12; Ch 2 - 0.59 - 0.12; Ch - 0.59 -	(P = 0. mbryo 1 153 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103 30 213 P = 2.3 (P = 0. Voman 122 53 370 P = 2.6 (P = 0.	3, df = 4 (P + 28) Transfer in O 71 8 8 9 5 223 2, df = 2 (P + 2 5, df = 4 (P + 26) 9 9 0, df = 2 (P + 26) 14 0, df = 2 (P + 26) 14 16 16 16 16 16 16 16 16 16 16	accept to the second se	scipients 6.2% 10.1% 8.5% 24.8% 24.8% 24.8% 24.8% 1.1% 1.7% 0.5% 2.9% 0.3% 6.6% 2.9% 0.3% 6.6% 2.9% 1.0% 1.0% 1.0% 1.0% 2.4% 2.4% 2.4% 2.4% 2.4% 2.4% 2.4% 2.4	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.91 (0.39, 2.15) 1.64 (0.84, 3.21) 0.79 (0.21, 2.90) 1.69 (0.43, 2.33) 1.11 (0.79, 1.36) 3.80 (1.10, 1.3.13) 1.55 (0.26, 9.20) 1.69 (0.43, 2.73)	
eterogenehy: Tau' est for overal effect 2.6 Clinical Pregn equeta 2019 attinez 2019 ubtotal (95% Cl) otal events eterogenehy: Tau' est for overal effect 2.7 Miscarriage R hethar 2019 hethar 2019 ubtotal (95% Cl) otal events eterogenehy: Tau' est for overall effect 2.8 Multiple Preg earn 2018 bio 2019 ann 2018 bio 2019 bio 2018 bio 2018 bio 2018 bio 2019 bio 2018 bio 201	= 0.02; ChA # 7 47 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101 101	(P = 0. mbryo 1 153 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103 30 213 P = 2.3 (P = 0. Voman 122 53 370 P = 2.6 (P = 0.	3, df = 4 (P + 2(P) Transfer in C 88 66 225 2, df = 2 (P + 2 5, df = 4 (P + 2 9 5, df = 4 (P + 2 9 0, df = 2 (P + 2 9 14 0, df = 2 (P + 2 9 14 0, df = 2 (P + 2 9 14 0, df = 2 (P + 2 14 16 18 18 18 10 10 10 10 10 10 10 10 10 10	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 = 0.67); 116 202 74 392 = 0.27); Embryo 155 Embryo 155 Embryo 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 155 166 155 166 167 167 167 167 167 167 167	scipients 6.2% 10.1% 8.5% 24.8% 12.4% 1.1% 1.7% 0.5% 2.9% 0.3% 6.6% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0%	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 1.079 (0.21, 2.23) 1.11 (0.79, 1.56) 3.60 (1.10, 13.13) 1.55 (0.26, 9.20) 1.09 (0.43, 2.73) 1.74 (0.78, 3.92] in Oocyte Recipients 2.19 (0.86, 5.63)	
eterogenehy: Tau' est for overal effect 2.6 Clinical Pregn egueia 2019 attrinez 2019 uibtotal (95% Cl) otal events eterogenehy: Tau' est for overal effect 2.7 Miscaria effect and 2019 wang 2019 wa	= 0.02; ChA 20; ChA 20	(P = 0. mbryo 1 153 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103 30 213 P = 2.3 (P = 0. Voman 122 195 53 370 P = 2.6 (P = 0. Voman 153 86	3, df - 4 (P - 4 28) Transfer in O 71 88 96 66 225 2, df - 2 (P - 77) 8 9 5 5 23 4 4 9 5 5 23 4 4 9 5 5 23 4 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 4 9 5 5 23 7 9 1 1 1 1 1 1 1 1 1 1 1 1 1	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 = 0.67); Embryo 116 202 74 392 = 0.27); Embryo 155 105 105 105 105 105 105 105	scipients 6.2% 10.1% 8.5% 24.8% 24.8% 24.8% 1.1% 1.7% 2.48% 2.48% 0.5% 2.48% 0.5% 2.9% 0.5% 2.9% 0.5% 2.6% Transfer 0.9% 2.6%	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 1.64 (0.84, 3.21) 0.79 (0.21, 2.90) 1.66 (0.64, 3.21) 0.63 (0.42, 3.23) 1.11 (0.79, 1.56) 3.80 (1.10, 13.13) 1.55 (0.26, 9.20) 1.09 (0.43, 2.73) 1.74 (0.78, 3.92] in Oocyte Recipients 2.19 (0.86, 5.63) 0.55 (0.50, 1.43)	
eterogenehy: Tau ² est for overall effect 2.6 Clinical Pregn gueria 2019 artinez 2019 likitz 2018 likitz 2019 likitz 2019 likitz 2019 likitz 2019 likitz 2019 likitz 2019 likitz 2019 likitz 2019	= 0.02; ChA 20; ChA 20	(P = 0. mbryo 1 153 154 86 393 P = 8.4. (P = 0. gnancy 48 13 19 103 30 213 P = 2.3. (P = 0. Woman 122 195 53 370 P = 2.6. (P = 0. Woman 122 135 154 155 155 155 155 155 155 15	3, df - 4 (P - 4 (P - 28) Transfer in O 71 8 8 66 225 2, df - 2 (P - 7 55 55 55 56) Undergoing 3 2 9 14 40, df - 2 (P - 7 18 9 54 9 14 10 10 10 10 10 10 10 10 10 10	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 = 0.67); 116 202 74 392 = 0.27); Embryo 155 Embryo 155 Embryo 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 146 155 155 166 155 166 167 167 167 167 167 167 167	scipients 6.2% 10.1% 8.5% 24.8% 12.4% 1.1% 1.7% 0.5% 2.9% 0.3% 6.6% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0%	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 1.079 (0.21, 2.23) 1.11 (0.79, 1.56) 3.60 (1.10, 13.13) 1.55 (0.26, 9.20) 1.09 (0.43, 2.73) 1.74 (0.78, 3.92] in Oocyte Recipients 2.19 (0.86, 5.63)	
eterogenehy: Tau ² est for overall effect 2.6 Clinical Pregn egueta 2019 attinez 2019 attinez 2019 ubtotal (95% Cl) otal events eterogenehy: Tau ² est for overall effect 2.7 Miscarriage R hethar 2019 hethar 2019 ubtotal (95% Cl) otal events eterogenehy: Tau ² eterogenehy: Tau ² ete	= 0.02; ChA 20; ChA 20	(P = 0. mbryo T 153 154 86 393 P = 8.4 (P = 0. gnancy 48 13 19 103 30 213 P = 2.3 (P = 0. Voman 122 195 53 370 P = 2.6 (P = 0. Voman 153 86 239	3, df - 4 (P + 28) Transfer in 0 88 66 225 2, df - 2 (P + 2 5, df - 4 (P + 2 9 5, df - 4 (P + 2 9 14 0, df - 2 (P + 2 9 14 16 16 16 16 16 16 16 16 16 16	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 = 0.67); Embryo 116 202 74 392 = 0.27); 105 105 105 105 106 107 107 108 109 109 109 109 109 109 109 109	xcipients 6.2N 10.1X 8.5X 24.8% 24.8% 24.8% 1.1N 2.48% 2.48% 2.48% 2.48% 0.5N 2.9% 0.3N 6.6% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 2.9% 0.3% 5.6% 7.7% 1.0% 7.7% 1.0% 7.7% 7.7% 7.7% 7.7% 7.7% 7.7% 7.7% 7	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 1.64 (0.84, 3.21) 0.79 (0.21, 2.90) 1.66 (0.64, 3.21) 0.63 (0.42, 3.23) 1.11 (0.79, 1.56) 3.80 (1.10, 13.13) 1.55 (0.26, 9.20) 1.09 (0.43, 2.73) 1.74 (0.78, 3.92] in Oocyte Recipients 2.19 (0.86, 5.63) 0.55 (0.50, 1.43)	
eterogenehy: Tau ² est for overal effect 2.6 Clinical Pregn egueta 2019 attrinez 2019 ubtotal (95% Cl) otal events eterogenehy: Tau ² est for overal effect 2.7 Miscarriage R hen 2019 wang 2019 w	= 0.02; ChA 20; ChA 20	(P = 0. mbryo 1 153 154 86 393 P = 8.4. (P = 0. gnancy 48 13 19 103 30 213 P = 2.3. (P = 0. Woman 122 195 53 370 P = 2.6. (P = 0. Woman 153 154 86 239 P = 2.3. 86 86 239 P = 3.0.	3, df = 4 (P + 28) Transfer in O 71 88 66 225 2, df = 2 (P + 2 5, df = 4 (P + 2 9 0, df = 2 (P + 2 14 0, df = 2 (P + 2 157) 14 0, df = 2 (P + 2 14 14 0, df = 2 (P + 2 157) 14 15 25 32 3 23 5 5 5 5 5 5 14 15 15 15 15 15 15 15 15 15 15	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 = 0.67); Embryo 116 202 74 392 = 0.27); 105 105 105 105 106 107 107 108 109 109 109 109 109 109 109 109	xcipients 6.2N 10.1X 8.5X 24.8% 24.8% 24.8% 1.1N 2.48% 2.48% 2.48% 2.48% 0.5N 2.9% 0.3N 6.6% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 2.9% 0.3% 5.6% 7.7% 1.0% 7.7% 1.0% 7.7% 7.7% 7.7% 7.7% 7.7% 7.7% 7.7% 7	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 1.64 (0.84, 3.21) 0.79 (0.21, 2.90) 1.66 (0.64, 3.21) 0.63 (0.42, 3.23) 1.11 (0.79, 1.56) 3.80 (1.10, 13.13) 1.55 (0.26, 9.20) 1.09 (0.43, 2.73) 1.74 (0.78, 3.92] in Oocyte Recipients 2.19 (0.86, 5.63) 0.55 (0.50, 1.43)	
eterogenehy: Tau ² est for overall effect 2.6 Clinical Pregn egueta 2019 attinez 2019 attinez 2019 ubtotal (95% Cl) otal events eterogenehy: Tau ² est for overall effect 2.7 Miscarriage R hethar 2019 hethar 2019 ubtotal (95% Cl) otal events eterogenehy: Tau ² eterogenehy: Tau ² ete	= 0.02; ChA 20; ChA 20	(P = 0. mbryo 1 153 154 86 393 P = 8.4. (P = 0. gnancy 48 13 19 103 30 213 P = 2.3. (P = 0. Woman 122 195 53 370 P = 2.6. (P = 0. Woman 153 154 86 239 P = 2.3. 86 86 239 P = 3.0.	3, df = 4 (P + 28) Transfer in O 71 88 66 225 2, df = 2 (P + 2 5, df = 4 (P + 2 9 0, df = 2 (P + 2 14 0, df = 2 (P + 2 157) 14 0, df = 2 (P + 2 14 14 0, df = 2 (P + 2 157) 14 15 25 32 3 23 5 5 5 5 5 5 14 15 15 15 15 15 15 15 15 15 15	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 = 0.67); Embryo 116 202 74 392 = 0.27); 105 105 105 105 106 107 107 108 109 109 109 109 109 109 109 109	xcipients 6.2N 10.1X 8.5X 24.8% 24.8% 24.8% 1.1N 2.48% 2.48% 2.48% 2.48% 0.5N 2.9% 0.3N 6.6% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 2.9% 0.3% 5.6% 7.7% 1.0% 7.7% 1.0% 7.7% 7.7% 7.7% 7.7% 7.7% 7.7% 7.7% 7	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 1.64 (0.84, 3.21) 0.79 (0.21, 2.90) 1.66 (0.64, 3.21) 0.63 (0.42, 3.23) 1.11 (0.79, 1.56) 3.80 (1.10, 13.13) 1.55 (0.26, 9.20) 1.09 (0.43, 2.73) 1.74 (0.78, 3.92] in Oocyte Recipients 2.19 (0.86, 5.63) 0.55 (0.50, 1.43)	
eterogenehy: Tau ² est for overal effect 2.6 Clinical Pregn egueia 2019 attrinez 2019 uibtotal (95% Cl) otal events eterogenehy: Tau ² est for overal effect 2.7 Miscarriage R hen 2019 wang 2019	= 0.02; ChA 20; ChA 20	(P = 0. mbryo 1 153 154 86 393 P = 8.4. (P = 0. gnancy 48 13 19 103 30 213 P = 2.3. (P = 0. Woman 122 195 53 370 P = 2.6. (P = 0. Woman 153 154 86 239 P = 2.3. 86 86 239 P = 3.0.	3, df = 4 (P + 28) Transfer in O 71 88 66 225 2, df = 2 (P + 2 5, df = 4 (P + 2 9 0, df = 2 (P + 2 14 0, df = 2 (P + 2 157) 14 0, df = 2 (P + 2 14 14 0, df = 2 (P + 2 157) 14 15 25 32 3 23 5 5 5 5 5 5 14 15 15 15 15 15 15 15 15 15 15	ocyte Re 155 146 105 406 = 0.01); 39 24 25 100 38 226 = 0.67); Embryo 116 202 74 392 = 0.27); 105 105 105 105 106 107 107 108 109 109 109 109 109 109 109 109	xcipients 6.2N 10.1X 8.5X 24.8% 24.8% 24.8% 1.1N 2.48% 2.48% 2.48% 2.48% 0.5N 2.9% 0.3N 6.6% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 2.9% 0.3% 5.6% 7.7% 1.0% 7.7% 1.0% 7.7% 7.7% 7.7% 7.7% 7.7% 7.7% 7.7% 7	1.09 (0.91, 1.30) 1.02 (0.82, 1.26) 0.93 (0.71, 1.21) 0.93 (0.71, 1.21) 1.64 (0.84, 3.21) 0.79 (0.21, 2.90) 1.66 (0.64, 3.21) 0.63 (0.42, 3.23) 1.11 (0.79, 1.56) 3.80 (1.10, 13.13) 1.55 (0.26, 9.20) 1.09 (0.43, 2.73) 1.74 (0.78, 3.92] in Oocyte Recipients 2.19 (0.86, 5.63) 0.55 (0.50, 1.43)	

Regarding ET outcomes (figure no. 3), none of the

studies reported live birth rate or ongoing pregnancy rate per woman starting stimulation.

Live birth rate (RR = 0.83, 95% CI = 0.39 to 1.78, two studies, 445 transfers) (18,21) and live birth or ongoing pregnancy rate per embryo transfer (RR =1.06 95% CI = 0.87 to 1.28, 6 studies, 1490 transfers) (4,18,19,20,21,22) were similar with progestins and GnRH agonists. Sensitivity analyses for trial design, short or long GnRH agonist protocol, MPA or MIP, ovarian reserve status suggested similar results.

DISCUSSIONS

This study suggests that progestins are capable of effectively preventing premature ovulation in ART cycles. Progestins seem to provide higher pregnancy rates than the short GnRH agonist protocol following frozen embryo transfers. Safety profile of progestins seems similar with GnRH analogues. However, the quality of evidence concerning their effectiveness with regard to oocyte yield and live birth rate in comparison to GnRH analogues is yet low and there is a strong need for more research.

The underlying assumptions of these analyses regarding the cost effectiveness were i) similar live birth rates with PPOS, the short GnRH agonist and GnRH antagonist protocols, and ii) 462 IU higher gonadotropin consumption with PPOS than the protocols using GnRH analogues. The increased cost of PPOS cycles were due to i) increased gonadotropin consumption and ii) the cost of additional monitoring and embryo thawing for the first transfer (even when the cost of freezing supernumerary embryos after the first fresh transfer in GnRH analogue protocols was assumed to balance out the cost of total embryo freezing in PPOS cycles).

The presence of a limited number of trials/studies, most of which are not randomized nor accounts for every woman starting stimulation are drawbacks, preventing definitive conclusions on the subject. However, we present an unbiased overview of the current literature and identify gaps in knowledge for future research. A reliable comparison between progestins and GnRH antagonists, the current standard of care for pituitary suppression is urgently needed, such as a comparison between flexible and the common PPOS.

Future Perspectives

An increasing number of studies suggest similar ROS and pregnancy outcomes per transfer with PPOS and GnRH analogues. MPA, DYG and MIP seem to be effective inhibitors of premature ovulation and provide similar quality oocytes as evidenced with pregnancy outcomes. Embryo euploidy rates as well as obstetric outcomes seem to be similar with PPOS and GnRH analogues. However, more high quality RCTs, comparing PPOS with both GnRH agonists and antagonists, which report live birth rates per woman starting stimulation, ideally in a cumulative manner, are needed from different centers and countries. Gonadotropin starting dosages and the requirements for dose adjustments must be pre-specified in these trials. Different progestins and PPOS protocols, e.g. fPPOS, require further assessment.

Avoiding GnRH analogue injections and taking progestin pills are assumed to be more convenient for the patients, however, none of the studies reported on side effects, or compared them with those in conventional OS cycles. Patient satisfaction should be properly assessed and compared in future studies. Different routes of administration or progestins, e.g. vaginal, transdermal, can be investigated.

Cost-effectiveness analyses based on local costs would be informative to assess the cost effectiveness of PPOS outside the U.S. with updated reliable information especially regarding gonadotropin consumption from good quality studies. Finally, more information on the course of pregnancy, obstetric

AMT, vol. 26, no. 1, 2021, p. 61

complications, neonatal and long-term infant outcomes, including health and development of children is needed.

CONCLUSIONS

In conclusion, if future high-quality trials confirm the assumptions of this review, progestins can become the agent of choice for pituitary suppression in ovarian stimulation cycles when a fresh embryo transfer is not intended, such as preimplantation genetic testing or fertility preservation cycles with oocyte or embryo cryopreservation. This would be a real benefit by eliminating the need for relatively costly GnRH analogues.

REFERENCES

- Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database Syst Rev. 2016;4:CD001750.
- 2. La Marca A, Capuzzo M. Use of progestins to inhibit spontaneous ovulation during ovarian stimulation: the beginning of a new era? Reprod Biomed Online; 2019.
- 3. Venetis CA, Kolibianakis EM, Bosdou JK, Tarlatzis BC. Progesterone elevation and probability of pregnancy after IVF: a systematic review and meta-analysis of over 60 000 cycles. Hum Reprod Update. 2013;19:433-457.
- 4. Shen X, Gao H, Chen Q, Cai R, Lyu Q, Wang Y, Wang L, Kuang Y. Effect of Switching from a Progestin-Primed Ovarian Stimulation Protocol to a Modified Ultra-Long Protocol Among Women Who Had 1 Progestin-Primed Ovarian Stimulation (PPOS) Failure Verses Those Who Had 2 PPOS Failures. Med Sci Monit; 2020;26: e918705.
- Franasiak JM, Olcha M, Shastri S, Molinaro TA, Congdon H, Treff NR, Scott RT, Jr. Embryonic aneuploidy does not differ among genetic ancestry according to continental origin as determined by ancestry informative markers. Hum Reprod. 2016;31:2391-2395.
- Humphries LA, Chang O, Humm K, Sakkas D, Hacker MR. Influence of race and ethnicity on in vitro fertilization outcomes: systematic review. Am J Obstet Gynecol. 2016;214:212 e211- 212 e217.
- Olcha M, Franasiak JM, Shastri S, Molinaro TA, Congdon H, Treff NR, Scott RT, Jr. Genotypically determined ancestry across an infertile population: ovarian reserve and response parameters are not influenced by continental origin. Fertil Steril. 2016;106:475-480.
- Begueria R, Garcia D, Vassena R, Rodriguez A. Medroxyprogesterone acetate versus ganirelix in oocyte donation: a randomized controlled trial. Hum Reprod. 2019;34:872-880.
- Chen Q, Chai W, Wang Y, Cai R, Zhang S, Lu X, Zeng X, Sun L, Kuang Y. Progestin vs. Gonadotropin-Releasing Hormone Antagonist for the Prevention of Premature Luteinizing Hormone Surges in Poor Responders Undergoing in vitro Fertilization Treatment: A Randomized Controlled Trial. Front Endocrinol (Lausanne). 2019;10:796.
- Eftekhar M, Hoseini M, Saeed L. Progesterone-primed ovarian stimulation in polycystic ovarian syndrome: An RCT. Int J Reprod Biomed (Yazd). 2019;17:671-676.
- Iwami N, Kawamata M, Ozawa N, Yamamoto T, Watanabe E, Moriwaka O, Kamiya H. New trial of progestin-primed ovarian stimulation using dydrogesterone versus a typical GnRH antagonist regimen in assisted reproductive technology. Arch Gynecol Obstet. 2018;298:663-671.
- 12. Mathieu d'Argent E, Ferrier C, Zacharopoulou C.

Outcomes of fertility preservation in women with endometriosis: comparison of progestin-primed ovarian stimulation versus antagonist protocols. J Ovarian Res. 2020;13:18.

- 13. Huang P, Tang M, Qin A. Progestin-primed ovarian stimulation is a feasible method for poor ovarian responders undergoing in IVF/ICSI compared to a GnRH antagonist protocol: A retrospective study. J Gynecol Obstet Hum Reprod. 2019;48:99-102.
- Martinez F, Rodriguez-Purata J, Clua E, Garcia S, Coroleu B, Polyzos N. Ovarian response in oocyte donation cycles under LH suppression with GnRH antagonist or desogestrel progestin: retrospective and comparative study. Gynecol Endocrinol. 2019;35:884-889.
- 15. Turkgeldi E, Yildiz S, Cekic SG, Shakerian B, Keles I, Ata B. Effectiveness of a flexible progestin primed ovarian stimulation protocol compared to the flexible GnRH antagonist protocol in women with decreased ovarian reserve. Human Fertility; 2020.
- Xiao ZN, Peng JL, Yang J, Xu WM. Flexible GnRH Antagonist Protocol versus Progestin-primed Ovarian Stimulation (PPOS) Protocol in Patients with Polycystic Ovary Syndrome: Comparison of Clinical Outcomes and Ovarian Response. Curr Med Sci. 2019;39:431-436.
- Yildiz S, Turkgeldi E, Angun B, Eraslan A, Urman B, Ata B. Comparison of a novel flexible progestin primed ovarian stimulation protocol and the flexible gonadotropinreleasing hormone antagonist protocol for assisted reproductive technology. Fertil Steril. 2019;112:677-683.
- Kuang Y, Chen Q, Fu Y, Wang Y, Hong Q, Lyu Q, Ai A, Shoham Z. Medroxyprogesterone acetate is an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. Fertil Steril. 2015;104:62-70.e63.
- Wang Y, Chen QJ, Wang NL, Chen H, Lyu QF, Kuang YP. Controlled Ovarian Stimulation Using Medroxyprogesterone Acetate and hMG in Patients With Polycystic Ovary Syndrome Treated for IVF A Double-Blind Randomized Crossover Clinical Trial. Medicine. 2016;95.
- 20. Xi Q, Tao Y, Qiu M, Wang Y, Kuang Y. Comparison Between PPOS and GnRHa-Long Protocol in Clinical Outcome with the First IVF/ICSI Cycle: A Randomized Clinical Trial. Clin Epidemiol. 2020;12:261-272.
- 21. Zhu X, Ye H, Fu Y. The Utrogestan and hMG protocol in patients with polycystic ovarian syndrome undergoing controlled ovarian hyperstimulation during IVF/ICSI treatments. Medicine (Baltimore). 2016;95:e4193.
- 22. Zhu X, Zhang X, Fu Y. Utrogestan as an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. Medicine (Baltimore). 2015;94: e909