Growth hormone cotreatment for poor responders undergoing in vitro fertilization cycles: a systematic review and meta-analysis

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Growth hormone cotreatment for poor responders undergoing in vitro fertilization cycles: a systematic review and meta-analysis

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Fertility and Sterility® Vol. 114, No. 1, July 2020 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2020.03.007

G.H. in reproductive medicine (All off-label)

- polycystic ovary syndrome
- Poor ovarian response
- advanced reproductive age
- poor oocyte or embryo quality

Mechanism of action

- Synthesis of insulin-like growth factor 1 (IGF-1), which binds to
  its own receptor
  insulin receptor

- In humans exerts distinct effects on
  early folliculogenesis
  oocyte maturation
  embryogenesis

Materials and methods

- Design: Systematic Rev according to PRISMA
- Studies published from 1985 to 2019 (Medline, Cochrane,….)
- Inclusion criteria: RCT, IVF with medication, poor responders
- Regardless of: definition of poor, GH addition protocol, type of gonadotropin
- Outcomes: LBR (>24 wk), CPR, OPR, abortion, oocyte n, viable embryo n

Results

- The 12 RCTs included
- 1,139 patients
- classified as poor responders according to different criteria
- 586 women that received GH in the previous cycle or during ovarian stimulation
- 553 women in comparison group
- Ten studies showed a significantly higher Clinical PR in the intervention group
- Four studies reported no significant different CPR /embryo transfer
- Significant higher total number of oocytes retrieved and MII oocytes in the GH group
- The GH group had more embryos available to transfer
- No difference was found in Miscarriage R or Ongoing PR

TABLE 1

General characteristic of randomized controlled trials included in the meta-analysis.

Author and year	Study design	Participants and main inclusion criteria	Ovarian stimulation (drugs and techniques)	Definition of poor ovarian response	Randomization method/blinding/ allocation concealment	Main outcomes
Owen et al. 1991	Single-center RCT	25 patients undergoing IVF: GH: 13; Control: 12; age <38 y; ≥1 IVF cycle with POR	• GnRH agonist 200 μg SC • hMG 225 IU/d • 5,000 UI hCG • oocyte retrieval 35 h after hCG administration • Luteal phase support with hCG 5,000 UI on day of ET	<6 oocytes previous cycle or <4 embryos developed	Randomization list/ double-blind/not reported	• Duration of hMG • Total dosage of hMG • No. of follicles ≥14 mm • No. of MII oocytes • Fertilization rate • No. of embryos • No. of oocytes • Pregnancy rate
Bergh et al. 1994	Multicenter RCT	40 patients undergoing IVF: I: placebo/placebo: 10; II: placebo/GH: 10; III: GH/GH: 10; IV: GH/placebo: 10; menstrual cycle length 25–35 d; BMI <28 kg/m^2	• GnRH agonist 1.2 mg/d intranasally or SC • hMG 225–300 IU/ d IM and/or human FSH 75–300 IU/d • oocyte retrieval 36–37 h fter hCG administration • Luteal phase support with hCG 1,250 IU every 3 days until day 12, or P 25 mg IM 2×/d	<5 oocytes retrieved previous IVF cycles	Not reported/double-blind/not reported	• Number of oocytes • Duration of hMG • Total dosage of hMG • E_2 levels • Endometrial thickness • No. of embryos • Pregnancy rate
Dor et al. 1995	Single-center RCT	14 patients undergoing IVF: GH: 7; Control: 7	• GnRH agonist 0.1 mg/d • hMG 300 IU or FSH 300 IU • oocyte retrieval 34–36 h after hCG administration	Previous IVF cycles: • E_2 level <501 pg/mL on day of hCG • <3 oocytes retrieved	Not reported/double-blind/identical-cover drug kit	• Total dosage of hMG • No. of oocytes • Fertilization rate • No. of embryos
Suikkari et al. 1996	Single-center RCT	22 patients undergoing IVF: GH: 16; Control: 6; age 25–40 y; BMI 19–27 kg/ m^2	• GnRH agonist 0.75 mg SC • urofollitropin 300 IU/d • oocyte retrieval 36 h from hCG administration	Previous IVF cycles: • ≤2 oocytes retrieved • ≥48 ampules of hMG consumed in a cycle	Not reported/double-blind/not reported	• Cancelation rate • Total dosage of FSH • E_2 levels • No. of oocytes • Fertilization rate • Implantation rate • Pregnancy rate

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TABLE 1

Continued.

Author and year	Study design	Participants and main inclusion criteria	Ovarian stimulation (drugs and techniques)	Definition of poor ovarian response	Randomization method/blinding/ allocation concealment	Main outcomes
Kucuk et al. 2008	Single-center RCT	61 patients undergoing ICSI: GH: 31; Control: 30	• GnRH agonist 0.1 mg/d • rFSH 450 IU	Poor response to high-dose gonadotropin treatment in first cycles in same center	Computer-generated randomization/not blind/sealed envelopes/	• Duration of stimulation • Total dosage of FSH • Cost of COS • E_2 levels • No. of MII oocytes • No. of embryos transferred • Pregnancy rate • Implantation rate
Eftekhar et al. 2012	Single-center RCT	82 patients undergoing IVF-ICSI: GH: 40; Control: 42; BMI $\leq$30 kg/m^2; no male infertility	• GnRH antagonist 0.25 mg/d when leading follicle 14 mm • hMG 300 IU/d -oocyte retrieval 34–36 h after hCG administration • Luteal phase support with P 100 mg/d IM	$\geq$1 previous failed IVF cycle, with $\leq$3 retrieved oocytes and $\leq$3 embryos obtained, and/or E_2 levels $<$500 pg/mL on day of hCG	Not reported/not blind/ sealed envelopes	• Duration of stimulation • Total dosage of hMG • Endometrial thickness • E_2 levels • Cancelation rate • No. of MII oocytes • No. of oocytes retrieved • No. of embryos • No. of embryos transferred • Fertilization rate • Implantation rate • Biochemical pregnancy rate • Clinical pregnancy rate • Miscarriage rate

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TABLE 1

Continued.

Author and year	Study design	Participants and main inclusion criteria	Ovarian stimulation (drugs and techniques)	Definition of poor ovarian response	Randomization method/blinding/ allocation concealment	Main outcomes
Bayoumi et al. 2015	Single-center RCT	172 patients undergoing IVF-ICSI: GH: 84; Control: 88; no previous ovarian surgery or male infertility	• GnRH agonist 0.05 mg SC • hMG 300–450 IU IM • Oocyte retrieval 35 h after hCG administration • ET ≤3 • Luteal phase support with vaginal P 800 mg/d and E_2 valerate 6 mg/d orally	Bologna criteria	Computer-generated randomization/not blind/sealed envelopes	• Total dosage of hMG • Duration of stimulation • Endometrial thickness • E_2 levels • No. of MII oocytes • Fertilization rate • No. of embryos transferred • Implantation rate • Chemical pregnancy rate • Clinical pregnancy rate • Cycle cancelation rate
Bassiouny et al. 2016	Single-center RCT	141 patients undergoing IVF-ICSI: GH: 68; Control: 73; no previous ovarian surgery	• GnRH antagonist 0.25 mg SC when leading follicle 12–14 mm • hMG 300–450 IU • oocyte retrieval 35 h after hCG administration • ET ≤3 • Luteal phase support with vaginal P 800 mg/d	Bologna criteria	Not reported/not blind/ sealed opaque envelopes	• Total dosage of hMG • Duration stimulation • Endometrial thickness • E_2 levels • No. of oocytes • No. of MII oocytes • Fertilization rate • No. of embryos transferred • Implantation rate • Chemical pregnancy rate • Clinical pregnancy rate • Early miscarriage rate • Ongoing pregnancy rate • Live birth rate

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TABLE 1

Continued.

Author and year	Study design	Participants and main inclusion criteria	Ovarian stimulation (drugs and techniques)	Definition of poor ovarian response	Randomization method/blinding/ allocation concealment	Main outcomes
Choe et al. 2017	Single-center RCT	127 patients undergoing IVF: GH: 62; Control: 65; menstrual cycle length 25–30 d; BMI <30 kg/m^2	• GnRH antagonist 0.25 mg/d SC when leading follicle 15 mm • rFSH 225–375 IU	Bologna criteria	Not reported/not blind/ not reported	• No. of oocytes • E_2 levels • Fertilization rate • Implantation rate • No. of MII oocytes • No. of good-quality embryos • Clinical pregnancy rate • Ongoing pregnancy rate • Miscarriage rate
Dakhly et al. 2018	Single-center RCT	240 patients undergoing IVF-ICSI: GH: 120; Control: 120; age <45 y; FSH <20 IU/L; no causes of infertility other than POR; no male infertility	• GnRH agonist 0.1–0.05 mg/d • rFSH 300 IU • Oocyte retrieval 35 h after hCG administration • ET ≤3 • Luteal phase support with vaginal P 800 mg/d	Bologna criteria	Computer-generated randomization/not blind/sealed opaque envelopes	• Duration of stimulation • Dosage of gonadotropins • E_2 levels • Endometrial thickness • No. of oocytes • No. of MII oocytes • Fertilization rate • Implantation rate • No. of transferred embryos • No. of frozen embryos • Canceled cycles • Chemical pregnancy rate • Clinical pregnancy rate • Miscarriage rate • Ongoing pregnancy rate • Live birth rate

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TABLE 1

Continued.

Author and year	Study design	Participants and main inclusion criteria	Ovarian stimulation (drugs and techniques)	Definition of poor ovarian response	Randomization method/blinding/ allocation concealment	Main outcomes
Safdarian et al. 2019	Single-center RCT	105 patients undergoing ICSI: GH: 70; Control: 35; no causes of infertility other than POR	• GnRH antagonist 0.25 mg/d SC when leading follicle >14 mm • rFSH 300–450 IU/d SC • Oocyte retrieval 36 h after hCG administration • ET ≤3 –Luteal phase support with vaginal P 800 mg/d	Bologna criteria	Computer-generated randomization table/single-blind/ not reported	• Total dosage of rFSH • Duration of stimulation • Endometrial thickness • No. of oocytes retrieved • No. of MII oocytes • Fertilization rate • No. of embryos transferred • Chemical pregnancy rate • Clinical pregnancy rate • Live birth rate
Norman et al. 2019	Multicenter RCT	130 patients undergoing ICSI: GH: 65; Control: 65; age <41 y; BMI ≤32 kg/m^2; FSH <15 IU/L; menstrual cycle 25–35 d; no endocrine disease; no AUB	• GnRH antagonist 0.25 mg/d SC when leading follicle >14 mm • Oocyte retrieval 36 h after hCG administration • Luteal phase support with vaginal P 800 mg/d	≤1 IVF cycle with ≤5 oocytes, with rFSH dosage >250 IU/d	Computer-generated randomization/ double-blind/ prenumbered drug kit	• Total dosage of rFSH • Duration of stimulation • No. of oocyte retrieved • Fertilization rate • No. of embryos transferred • No. of embryos cryopreserved • Quality of embryos obtained • Miscarriage rate • Live birth rate

Note: AUB = abnormal uterine bleeding; BMI = body mass index; COS = controlled ovarian stimulation; ET = embryo transfer; GH = growth hormone; IM = intramuscularly; IVF = in vitro fertilization; MII = metaphase II; POR = poor ovarian response; RCT = randomized controlled trial; SC = subcutaneously.

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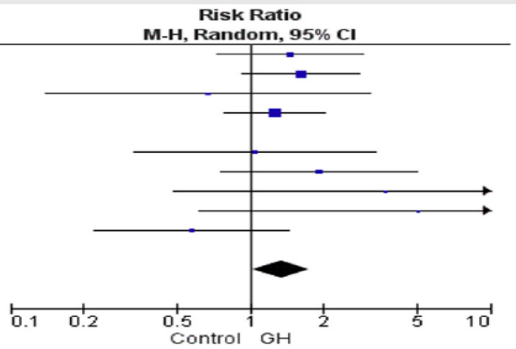
FIGURE 1

Study or Subgroup	GH Events	GH Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bassiouny et al, 2016	15	68	11	73	15.1%	1.46 [0.72, 2.96]
Bayoumi et al,2015	24	72	15	73	24.1%	1.62 [0.93, 2.83]
Bergh et al, 1994	2	10	3	10	3.1%	0.67 [0.14, 3.17]
Dahkly et al, 2018	29	120	23	120	31.8%	1.26 [0.78, 2.05]
Dor et al, 1995	0	7	0	7		Not estimable
Eftekhar et al, 2012	5	40	5	42	5.5%	1.05 [0.33, 3.35]
Kucuk et al, 2008	10	31	5	30	8.3%	1.94 [0.75, 5.00]
Owen et al, 1991	4	13	1	12	1.8%	3.69 [0.48, 28.57]
Safdarian et al, 2019	5	35	1	35	1.7%	5.00 [0.62, 40.64]
Seung-Ah et al, 2017	6	62	11	65	8.6%	0.57 [0.23, 1.45]
Total (95% CI)		**458**		**467**	**100.0%**	**1.34 [1.02, 1.77]**
Total events	100		75			

Heterogeneity: Tau² = 0.00; Chi² = 7.76, df = 8 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)



Growth hormone (GH) cotreatment versus conventional controlled ovarian stimulation (Control): clinical pregnancy rate. CI = confidence interval; M-H = Mantel-Haenszel.

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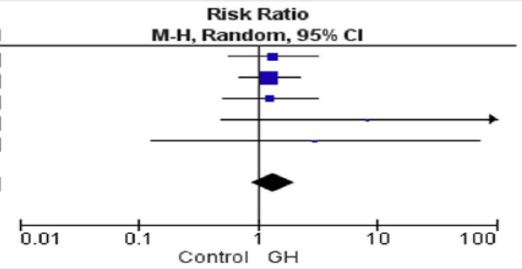
FIGURE 2

Study or Subgroup	GH Events	GH Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bassiouny et al, 2016	10	68	8	73	23.6%	1.34 [0.56, 3.20]
Dahkly et al, 2018	21	120	17	120	51.6%	1.24 [0.69, 2.22]
Norman et al, 2019	9	65	7	64	20.8%	1.27 [0.50, 3.19]
Owen et al, 1991	4	13	0	12	2.2%	8.36 [0.50, 140.56]
Safdarian et al, 2019	1	35	0	35	1.8%	3.00 [0.13, 71.22]
Total (95% CI)		**301**		**304**	**100.0%**	**1.34 [0.88, 2.05]**
Total events	45		32			

Heterogeneity: Tau² = 0.00; Chi² = 2.00, df = 4 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)



Growth hormone (GH) cotreatment versus conventional controlled ovarian stimulation (Control): live birth rate. CI = confidence interval; M-H = Mantel-Haenszel.

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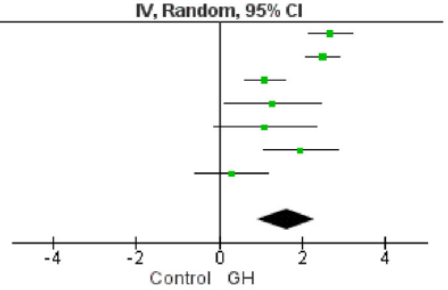
FIGURE 3

A

Study or Subgroup	GH Mean	GH SD	GH Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bassiouny et al, 2016	7.58	1.4	68	4.9	1.78	73	16.2%	2.68 [2.15, 3.21]
Bayoumi et al,2015	7.2	1.5	84	4.7	1.2	88	16.8%	2.50 [2.09, 2.91]
Dahkly et al, 2018	5.4	1.7	120	4.3	2.1	120	16.4%	1.10 [0.62, 1.58]
Eftekhar et al, 2012	6.1	2.9	40	4.8	2.4	42	11.9%	1.30 [0.14, 2.46]
Norman et al, 2019	5.2	3.5	65	4.1	3.7	65	11.3%	1.10 [-0.14, 2.34]
Safdarian et al, 2019	7.14	2.03	35	5.17	1.82	35	13.7%	1.97 [1.07, 2.87]
Seung-Ah et al, 2017	3.7	2.6	62	3.4	2.5	65	13.8%	0.30 [-0.59, 1.19]
Total (95% CI)			**474**			**488**	**100.0%**	**1.62 [0.94, 2.31]**

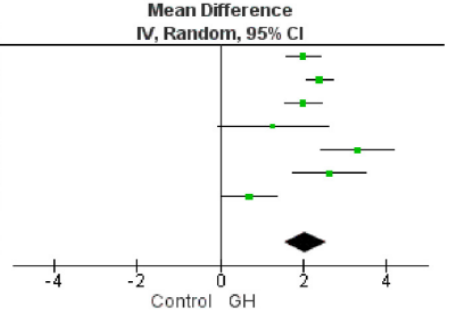
Heterogeneity: Tau² = 0.69; Chi² = 42.42, df = 6 (P < 0.00001); I² = 86%
Test for overall effect: Z = 4.63 (P < 0.00001)



B

Study or Subgroup	GH Mean	GH SD	GH Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bassiouny et al, 2016	4.53	1.29	68	2.53	1.18	73	17.5%	2.00 [1.59, 2.41]
Bayoumi et al,2015	5.2	1.2	84	2.8	1	88	18.2%	2.40 [2.07, 2.73]
Dahkly et al, 2018	4.1	2.1	120	2.1	1.4	120	17.1%	2.00 [1.55, 2.45]
Eftekhar et al, 2012	5.57	3.2	40	4.29	3.01	42	8.1%	1.28 [-0.07, 2.63]
Kucuk et al, 2008	6.5	2.1	31	3.2	1.4	30	12.1%	3.30 [2.41, 4.19]
Safdarian et al, 2019	6.09	1.65	35	3.46	2.09	35	12.3%	2.63 [1.75, 3.51]
Seung-Ah et al, 2017	2.5	2	62	1.8	1.8	65	14.7%	0.70 [0.04, 1.36]
Total (95% CI)			**440**			**453**	**100.0%**	**2.06 [1.56, 2.56]**

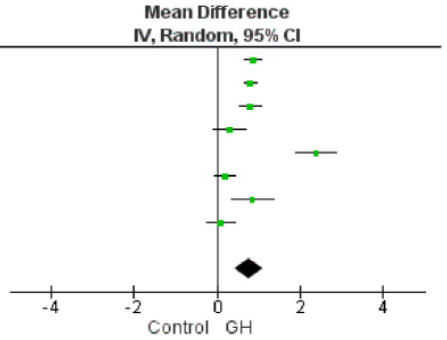
Heterogeneity: Tau² = 0.33; Chi² = 30.46, df = 6 (P < 0.0001); I² = 80%
Test for overall effect: Z = 8.07 (P < 0.00001)



C

Study or Subgroup	GH Mean	GH SD	GH Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bassiouny et al, 2016	2.89	0.45	68	2.03	0.81	73	13.5%	0.86 [0.65, 1.07]
Bayoumi et al,2015	2.9	0.3	84	2.1	0.6	88	13.9%	0.80 [0.66, 0.94]
Dahkly et al, 2018	2.4	0.9	120	1.6	1.1	120	13.2%	0.80 [0.55, 1.05]
Eftekhar et al, 2012	2.6	0.9	40	2.3	0.93	42	11.9%	0.30 [-0.10, 0.70]
Kucuk et al, 2008	3.3	1.2	31	0.9	0.7	30	10.9%	2.40 [1.91, 2.89]
Norman et al, 2019	1.3	0.7	65	1.1	0.7	65	13.3%	0.20 [-0.04, 0.44]
Safdarian et al, 2019	2.49	0.66	35	1.63	1.39	35	10.7%	0.86 [0.35, 1.37]
Seung-Ah et al, 2017	1.7	0.9	62	1.6	1	65	12.5%	0.10 [-0.23, 0.43]
Total (95% CI)			**505**			**518**	**100.0%**	**0.76 [0.43, 1.10]**

Heterogeneity: Tau² = 0.20; Chi² = 84.20, df = 7 (P < 0.00001); I² = 92%
Test for overall effect: Z = 4.48 (P < 0.00001)



Growth hormone (GH) cotreatment versus conventional controlled ovarian stimulation (Control): (**A**) total number of the oocytes, (**B**) number of metaphase II oocytes, (**C**) number of embryos available to transfer. CI = confidence interval; M-H = Mantel-Haenszel.

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Discussion

- The present meta-analysis evaluated 1,139 patients, which represents a significant increase compared with the latest previous meta-analysis following the PRISMA criteria (hum reprod update 2009) (^ CPR and LBR)
- GH may increase clinical pregnancy rates (n= 1139; 12 studies), but with no effect on live birth rates (n= 605; 5 studies). Thus, it seems premature to recommend the use of GH as a valid option for poor responders.
- substantially higher cost of treatments including GH administration
-

Heterogeneity:

- definition of poor ovarian response
- GH cotreatment regimen
- protocol used for ovarian stimulation
- protocol used for luteal phase support

Mechanism of action

- GH produced more oocytes and embryos. Thus, GH might improve follicular FSH responsiveness.
- Some studies included in this meta-analysis reported lower gonadotropin doses.
- GH receptors on granulosa, theca, and luteal cells, thus promoting steroidogenesis

and gametogenesis.

- increases the number of functional mitochondria in oocytes of older patients, which may play an important role in female fertility and ART

Future RCTs should take into account

not only the ovarian response and IVF outcomes, but also

- safety profile for mothers
- neonatal outcomes
- risk of birth defects with the use of GH cotreatment
- proper cost-effectiveness analysis [4,652.5 USD # 2,272 USD (P<.001)]

An example for safety profile

Administration of supraphysiologic levels of GH might induce transient DNA damage and mitogenic impairment in human lymphocytes

CONCLUSION

- GH supplementation in poor ovarian responders undergoing IVF cycles might improve clinical pregnancy rates without affecting the live birth rate, miscarriage rate, and ongoing pregnancy rate.
- It is still premature to recommended GH cotreatment for poor responders.
- detailed cost-effectiveness analysis is urged.
- Evaluation of birth defects should be taken into account in future studies.

Thank’s for your attention

اسلاید

در لینک زیر http://vrhrc.tums.ac.ir/

G.H. in reproductive medicine

- polycystic ovary syndrome
- Poor ovarian response
- advanced reproductive age
- poor oocyte or embryo quality

G.H. is FDA approved for

- short bowel syndrome
- growth hormone deficiency
- musclewasting disease associated with HIV/AIDS

Administration of G.H. for IVF

- Daily injection of 4 IU (1- 12 IU/day) from day 21 of previous cycle until the day of hCG injection
- Har pen: 5 mg.

Azad: 145000 toman

Bimeh: 25000 toman (8 adad dar har noskheh)

Key Performance Indicator

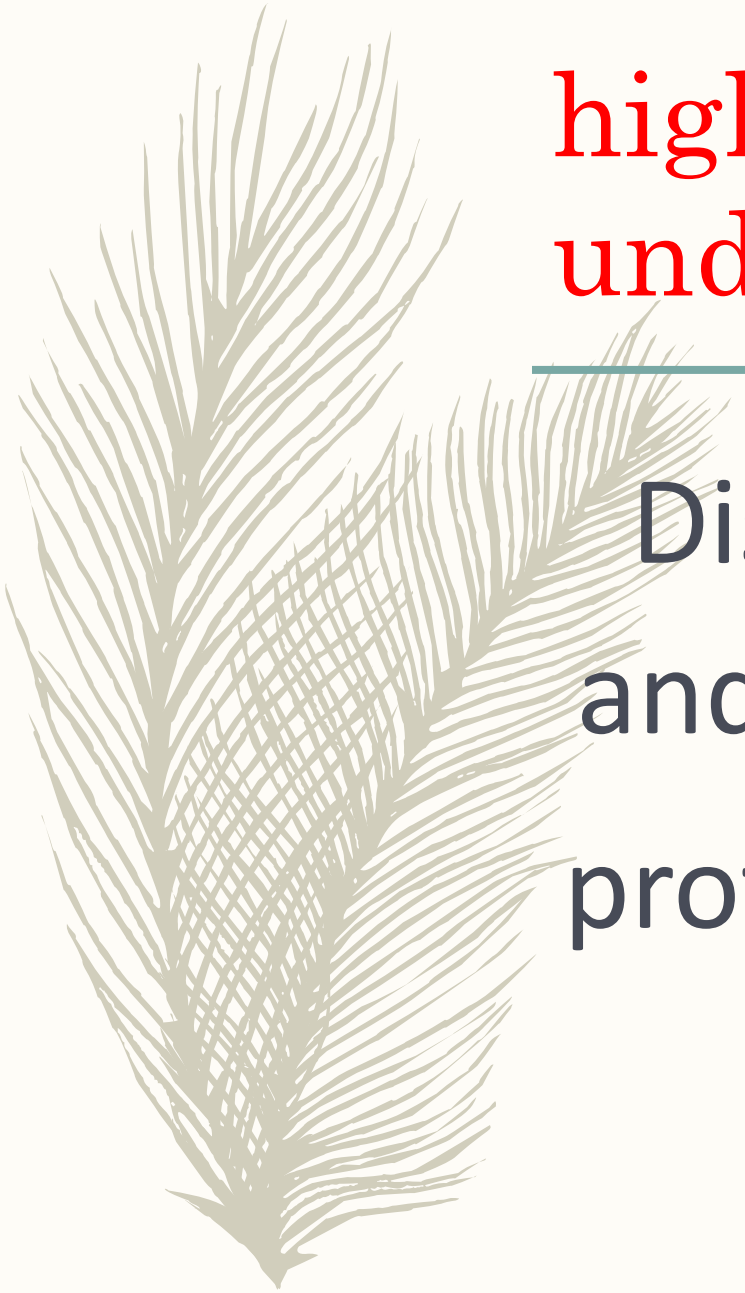
- GH may increase clinical pregnancy rates (n= 1139; 12 studies), but with no effect on live birth rates (n= 605; 5 studies). Thus, it seems premature to recommend the use of GH as a valid option for poor responders.
- CPR: more accurate
- LBR: better KPI, more clinically relevant

Debate

although CPR seemed to be higher in the intervention group, per embryo transfer did not detect any difference

the embryos in the GH group had greater implantation potential

the CPR reflects the higher number of embryos available to transfer



high heterogeneity
underpowered subgroup analysis

Disability to identify a standard and efficient GH supplementation protocol, even though GH seemed to affect CPR