MANAGEMENT
Recurrent Implantation Failure

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Infertility Fellowship

Avicenna

Multidisciplinary Approach

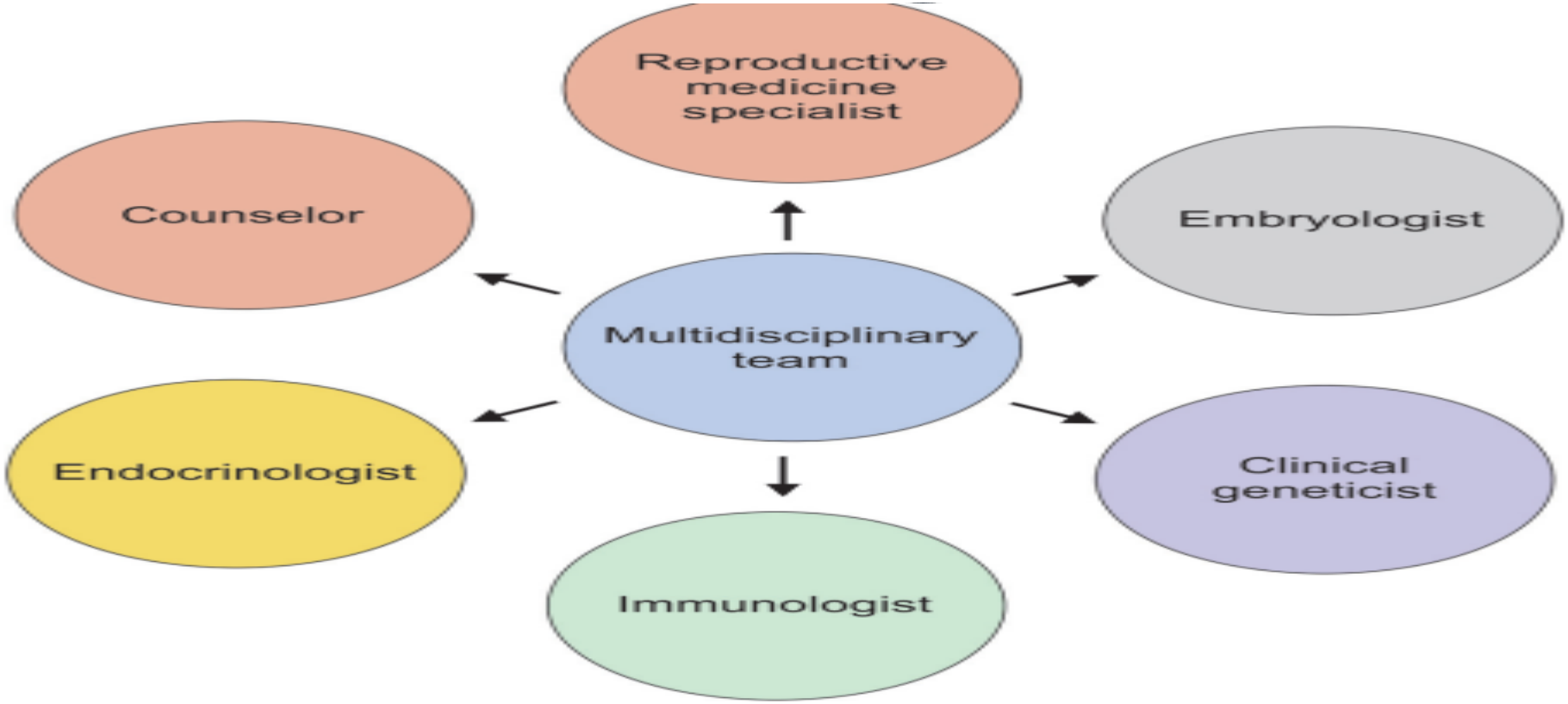
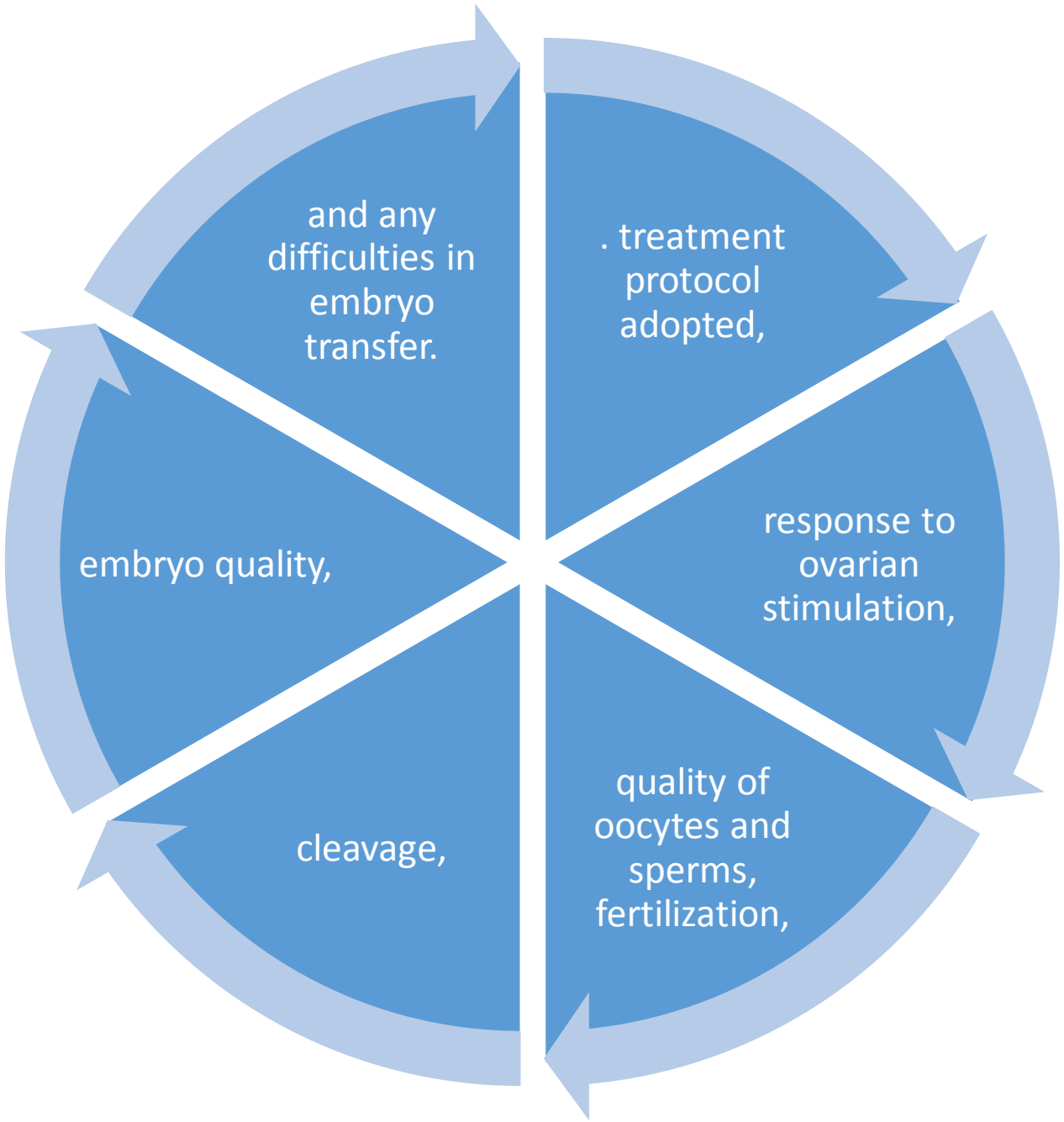


Fig. 5: Multidisciplinary team: reproductive medicine specialist, embryologist, counselor, clinical geneticist, immunologist, and endocrinologist.

- زوج باRIFتوسط این تیم ارزیابی می شود باید یک **پروتکل محلی** وجود داشته باشد
- این تیم در مورد چگونگی بررسی این موارد توافق کرده است
- . در حین ارزیابی ، تیم باید **تمام جزئیات** را بررسی کند
- موردی که شامل **علت** ناباروری است ،، **پروتکل درمان** ، **پاسخ** به تحریک تخمدان
- ، ***کیفیت تخمک ها و اسپرم ها*** ، **لقاح** ،
- برش ، **کیفیت جنین** و هر گونه مشکل در**انتقال** جنین


. treatment protocol adopted,
response to ovarian stimulation,
quality of oocytes and sperms, fertilization,
cleavage,
embryo quality,
and any difficulties in embryo transfer.

- این مشاوره با تیم چندرشته ای **"خاص" "special”**است و نباید مانند سایر بیماران سرپایی معمول باشد
- به زوج باید فرصت کافی داده شودمشکلات و مسائل خود را مطرح کنید و تیم باید با آنها همدل باشد
- توضیح در آن بسیار مهم است توضیح جزئیات **علت اصلی ناباروری** ،
- Couple should also Be explained **about further plan** of action and the scientific rationale behind this plan.
- و**احتمال موفقیت** را در تحقیقات بیشترتوضیح دهید
- درمان اگر احتمال موفقیت بسیار کم باشد ، آنها باید در مورد **گزینه های جایگزین** از جمله توضیح داده **شود اهدای گامت** ، **gamete donation, gestational surrogacy or even adoption یا حتی فرزندخواندگی**

- **شکست مکررلانه گزینی** ، **منبع ناراحتی** است و نارضایتی هم برای بیماران و هم برای پزشکان. این غیر معمول نیست که احساس تنفر از تکرار داشته باشید

- شکست ها گاهی اوقات توضیح در مورد آن بسیار دشوار می شود چگونه انتقال بلاستوسیست یوپلوئید در اندومتر به ظاهر طبیعی ناموفق بود

- . در این شرایط ، پزشکان شروع به انجام بااعمال ، با فقدان شواهد قوی درجمعیت آسیب پذیر می کنند ، که برای هر کاری آماده هستند به یک بارداری برسد

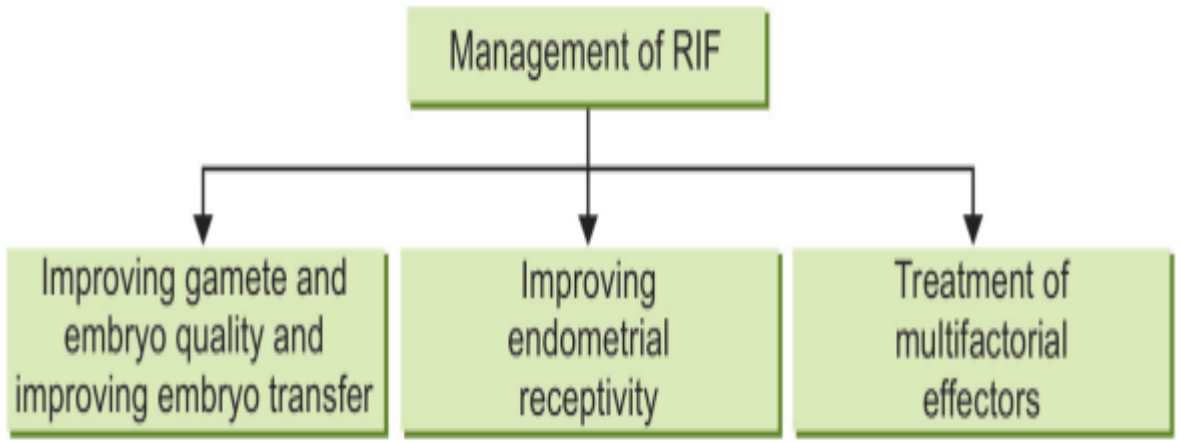
- بنابراین داشتن رویکرد چند رشته ای مهم است مراقبت و درمان مبتنی بر شواهد در، باید به بیماران مشاوره داده شود

- استراتژی ها ، باید در **مورد شیوه زندگی** تأکید شود

- تغییرات شامل حفظ BMI،

- ترک سیگار و الکل احتمال موفقیت درمان را افزایش می دهد

Flowchart 5: Management of recurrent implantation failure.



Treatment of Poor Oocyte Quality

- در برخی از بیماران ممکن است RIFبه دلیل مشکلات در کیفیت تخمک یا به دلیل عدم بهینه بودن آنها
- تحریک از نظر تعداد تخمک کمتر، دوز گنادوتروپین را می توان افزایش داد هیچ پروتکل خاصی برتر نیست
- افزودن LHدر پاسخ دهندگان ضعیف و همچنین در زنان بالای 35 سال مفید است
- و در زنان با اندومتریوز ، GnRHآگونیست ها 3 تا 6 ماه قبل از کنترل تحریک تخمدان

- استفاده از annexin-V هیالورونیک اسید ((HA
- کاهش تعداد اسپرم ها با افزایش شاخص تجزیه DNA (DFI)
- روش انتخاب اسپرم HA احتمالاً پتانسیل را کاهش می دهد
- عوارض ژنتیکی و اثرات نامطلوب سلامت عمومی تزریق داخل سیتوپلاسمی اسپرم ICSI) 108)
- انتخاب اسپرمهای غیر آپوپتوز با طبقه بندی سلولهای مغناطیسی
- ((MACSممکن است برای افزایش نتایج لقاح آزمایشگاهی استفاده شود
- با افزایش نفوذ اسپرم-تخمک

- Assisted hatching (AH) سه مکانیسم ممکن چگونه کاشت کمک کند:
- • روش هایی مانند IVF، کشت سلولی یا سرمازدگی می تواند باعث سخت شدن زونا شود
- • برای تبادل متابولیتها ، عوامل رشد ، ایجاد شده از طریق AHمی تواند به عنوان یک کانال باز شدن عمل کند.

- دریافت که
- هیچ تاثیری بر "نرخ خانه به نوزاد" وجود نداشت . AHافزایش قابل توجهی در CPRو حاملگی چند قلویی داد
- ، اما در 15 RCTکه به نرخ LBRنگاه کردند ، شواهدی از تفاوت بین AHو گروه کنترل
- هیچ موردی وجود نداشت

Co-culture:

- فرضیه علمی شامل ، ترشح عوامل جنینی مانند
- مواد مغذی ، عوامل رشد و سایتوکاین ها و سم زدایی
- رادیکالهای آزادکشت همزمان آندومتر در 1030 بیمار مبتلا به RIFو
- ٪49 PRاسپندورفر و همکاران مطالعه کرد

Preimplantation genetic screening (PGS)

(در دهه 1990 هزاران IVFبعد از بیوپسی یک نمونه انجام شد

- **بلاستومر از روز سوم** مرحله cleavageو تجزیه و تحلیل نرمال بودن **5** کروموزوم از طریق فلورسنت در هیبریداسیون درجا (FISH
- بعداً RCTها نشان دادند کهPGS یاCPR یاLBRرا افزایش نداد و در برخی موارد کاهش یافت

- به دلایل زیر است که PGSبا روز 3 جنین ممکن است موثر نباشد:
- **محدودیت دقت FISH**
- **تعداد محدودی سلول** برای تجزیه و تحلیل در دسترس است
- جنین های روز سوم در اوج **ناهنجاری کروموزومی و موزاییسم** هستند

- با ظهور فناوری های جدید ، جامع غربالگری کروموزوم ((CCSدر جنین روز 5 امکان پذیر است
- بیوپسی سلولهای تروفکتودرم فرضیه علمی که CCSمی تواند لانه گزینی را افزایش دهد
- میزان ، کاهش زمان بارداری ، کاهش RPLو .RIFدرحال بررسی است

Mitochondrial DNA load measurement (mitoscore)

- تخمین زده شده است **که تخمک های متافاز IIدارای 105 DNAمیتوکندریایی** (mtDNA) کپی هستند
- این کپی ها هستندکه بر روی سلولهای cleaving cells به عنوانreplication of
- mtDNAتقسیم می شوند
- **mtDNAتا مرحله بلاستوسیست** رخ نمی دهد.
- مطالعات گزارش ارتباط **بین mtDNAبالاتردر بلاستوسیستها و پتانسیل کاشت کمتر** را نشان می دهد
- این می تواند به دلیل اختلال در تامین انرژی باشد و استرس متابولیک بالاتر در جنین با میتوسکور بالاتر
- .در حال حاضر هیچ مطالعه ای وجود ندارد که ارتباط میزان پایین تری میتوسکوربا LBR بهبود یافته را نشان دهد

Time-lapse imaging and metabolomics:

- همانطور که گفته شد قبلا Time-lapseنمی تواند به عنوان جانشین استفاده شود
- برای PGS65و مطالعات مختلف این را نشان داده است
- morphokineticsو omicsرویکردهای مکمل برای ارزیابی زنده ماندن جنین هستند

Improving Embryo Transfer Ultrasound-guided Embryo Transfer

- سونوگرافی شکمی (TA-US)تکنیک انتقال جنین هدایت شده تکنیکی است که به طور گسترده مورد مطالعه قرار گرفته
- ***تفاوت در CPR، LBR در TV-U و TA-US. پیدا نشد***
- newer techniques like transvaginal ultrasound guidance (TV-US) for embryo transfer, 3D ultrasound, uterine length measurement before transfer (ULMbET) have not been studied
- آن فقط شواهد ضعیفی در مورد حاملگی خارج رحمی و میزان سقط جنین ارائه می دهد
- the literature focus is mostly on day 2–3 embryo transfers, making the applicability of the results to day 5 transfers difficult

Embryo Glue and Adherence Compounds

- استفاده از سیلانت های فیبرین برای بهبود LBRو کاهش خارج رحمی حاملگی پیشنهاد شد اما بهبود چشمگیر در نتیجه بالینی خوب نشان نداد
- گزارش شده است اسید هیالورونیک (HAبه طور طبیعی دردستگاه تولید مثل زنان وجود دارد و محلول چسبناکی را تشکیل می دهد که می تواند به کاشت کمک کند

- استفاده از یک محیط انتقال جنین خاص غنی شده با HA.
- Cochrane review by Bontekoe et al. 2014 included 17 RCTs with 3,898 participants, demonstrating ***moderate quality evidence for an improvement in CPR and LBR and an associated increase in multiple pregnancy rate***
- شواهد متناقض ، است
- انجام RCTهای بیشتر برای اثربخشی ارزیابی HAبه عنوان یک ترکیب چسبندگی در هنگام انتقال جنین
- ضروری است

Sequential Embryo Transfer

- The possible disadvantage of this strategy is that the second insertion
- of the catheter **can cause trauma to the endometrium or**
- **stimulate the secretion of prostaglandins** which could initiate
- uterine contractions.
- It could also cause additional microbial contamination and introduce
- more mucus into the uterine cavity thus affecting implantation.

- The possible **advantage** of sequential embryo transfer is that this
- interval embryo transfer could affect the ***endometrial cavity in a***
- ***positive manner by inducing factors that enhance implantation***.

- Double embryo transfer which happens with **sequential embryo**
- **transfer can be beneficial in women with RIF.**
- There are conflicting evidences with regard to sequential embryo
- transfers where a few studies support its useand others do not

Freeze All Strategy

- یک استراتژی منجمد کردن یک روش جدید است که اخیراً در آن ایجاد شده است ه به
- منظور حفظ انجماد همه جنین ها پس از یک ICSIو به دنبال آن FETانجام می شود

- Currently freeze-all strategy is adopted in **hyperresponders,**
- **agonist trigger, along with PGS**

- Assessments of secondary measures found **significant differences**
- **in pregnancy rate, implantation rate, and clinical pregnancy**
- **rate, all supporting the freeze-all group, but no significant**
- **difference in the rate of early pregnancy loss.**
- .

- The rate of **multiple pregnancy in** the freeze-all group was
- significantly **higher** than in the fresh group, telling that, in regular
- clinical practice, the **number of embryos** transferred should be
- **decreased** in order to compensate for the higher implantation rate
- (40.0% vs 16.0%) with thawed embryos than with fresh embryos in
- these patients

- Another strong indication for freeze-all strategy in RIF patients is when **the embryos have been subjected to PGS.**
- The fresh blastocyst transfer approach after PGS necessitates not only availability of **expanded blastocysts onthe morning of day 5**, but also one of these **being euploid, necessitating embryo transfer**.

- Contrary to this in freezeall strategy both day **5 and day 6 embryos**
- can be biopsied, and the **whole cohort** of embryos can be
- cryopreserved, enabling patients to have their embryo transfer at a
- later date
- . Study by Semra Kahraman150 at Istanbul Hospital, Turkey analyzed a
- total of 1,486 cycles and found that all **positive outcomes,**
- **implantation, ongoing pregnancy rate and LBR were**
- **significantly higher in freeze-all group.**

- In cases with advanced maternal age **(38–43 years), ongoing pregnancy rate and LBR were significantly higher in freeze-all group** and this is possibly related **to endometrial receptivity**, as it is probable that in **older women the quiet endometrium** is more crucial.
- Furthermore it **decreases the pressure in embryology laboratory** as it permits more plasticity regarding the scheduling of embryo biopsy and also having the biopsy results of the whole cohort at the same time permits inclusion of all blastocysts

- انعطاف پذیری در مورد زمانبندی بیوپسی جنین و همچنین نتایج بیوپسی کل گروه در
- در همان زمان اجازه می دهد تا همه بلاستوسیست ها وارد شوند

Zygote Intra-Fallopian Transfer

- Human tubal fluid contains ***several growth factors and cytokines***
- ***which aid in the development of the embryo making it competent for implantation***.
- However meta-analysis by Habana and Palter151 has reported similar
- pregnancy and implantation rates in ZIFT and intrauterine transfer
- groups **(36.5% vs 31.4% and 15% vs 12%** respectively.
- At present, with improvedculture conditions in ART**, intrauterine**
- **transfer remains the technique of choice in women with RIF.**

Improving Endometrial Receptivity
Treatment of Uterine Abnormalities

.

- Uterine septum Operative hysteroscopy (HSC) and septal resection **Increases implantation**
- **rate Decreases miscarriage rate**
- **Increases term delivery rates**

- Tomaževič et al. (2010) performed a retrospective matched-control study in IVF/intracytoplasmic sperm injection (ICSI) patients studying 289 embryo transfer before HSC and 538 embryo transfer following HSC. A control group consisted of 1,654 embryo transfers with normal uterus. However, in spite of these impressive results in favor of surgery before IVF/ICSI, **PR and LBR remained low (15–20% and ≤3%, respectively) and MRs were high (77%) in nonoperated patients compared with other published data**, and therefore these results should be interpreted with caution
-

- Others have not observed lower PRs, but ***have detected increased***
- ***miscarriage and reduced term delivery rates in women***
- ***with uncorrected septate*** and **bicornuate uterus** undergoing IVF
- According to **ASRM 2016**, there is **limited evidence** to suggest septal
- resection would increase LBR in women with infertility or prior pregnancy loss

- طبق ASRM 2016، شواهد محدودی وجود دارد
- برداشتن septum باعث افزایش LBRدر زنان مبتلا به ناباروری یاpregnancy loss
- قبلی می شود

Polyps Hysteroscopic

- Polypectomy Improvement in pregnancy rate, **both spontaneous and assisted**
- Meta-analysis supports a benefit with the hysteroscopic removal of
- polyps. If **28%** of women become pregnant in the **control** group, the
- evidence suggests that between **50% and 76%** of women will become
- pregnant after **the removal of the endometrial polyps**

Submucosal fibroids and intramural fibroids protruding into the endometrial cavity

- • Myomectomy Improvement in **implantation rate, CPR and LBR**
- • Decrease **in miscarriage rate**
- The presence of a **submucous** fibroid in women with RIF, regardless
- of the size, and fibroids **protruding into** the endometrial cavity should
- be **removed** as it is shown in various studies that removal improves
- **reproductive outcome**

- Somigliana et al. (2011) studied 119 women with **asymptomatic**
- **intramural or subserosal fibroids, 5 cm** and compared
- these outcomes with 119 controls:

- The live birth rates **were similar** **(18% versus 13%,** respectively),

- and the adjusted odds ratio (OR) was 1.45 (95% CI: 0.71–2.94).

- • Yan et al. (2014) included 249 women undergoing their first IVF/ ICSI
- cycle with **different types of fibroids** and compared them with 249
- controls **without fibroids**.
  - After matching for several variables, delivery rates were **33.7% and**
  - **30.5**% for controls and women with fibroids, respectively [adjusted
- OR 1.03 (95% CI: 0.95–1.11)] A ***significant negative effect*** on delivery
    - rate was noted when the **largest tumor diameter was 2.85 cm**

Adenomyosis Depot GnRHa alone or in combination with cytoreductive surgery

- • **GnRHa—regression** of lesions through induction hypogonadotropic Status •
- Direct action on adenomyotic lesions through types **I and II receptors**
- **on the endometrium**
- • **Cytoreductive surgery** *reduces hypertrophy* and subsequently
- improves **function by bringing the uterinelayers** closertogether.

- It also **enhances bloodsupply**, therebyfacilitating GnRHa Action With respect to pregnancy outcomes with GnRHa, Wang et al. (2009) retrospectively studied two groups of women.

- In the first group, adenomyotic tissue was *surgically removed and GnRHa was given for 6* months (n = 28). A second group (n = 37) only received *6 months of GnRHa.*

- They noted **uterine regrowth** after the effect of GnRHa had disappeared in the GnRHa-only group.

- Cumulative spontaneous PRs after 36 months were significantly higher with the **combined treatment** of surgery plus GnRHa

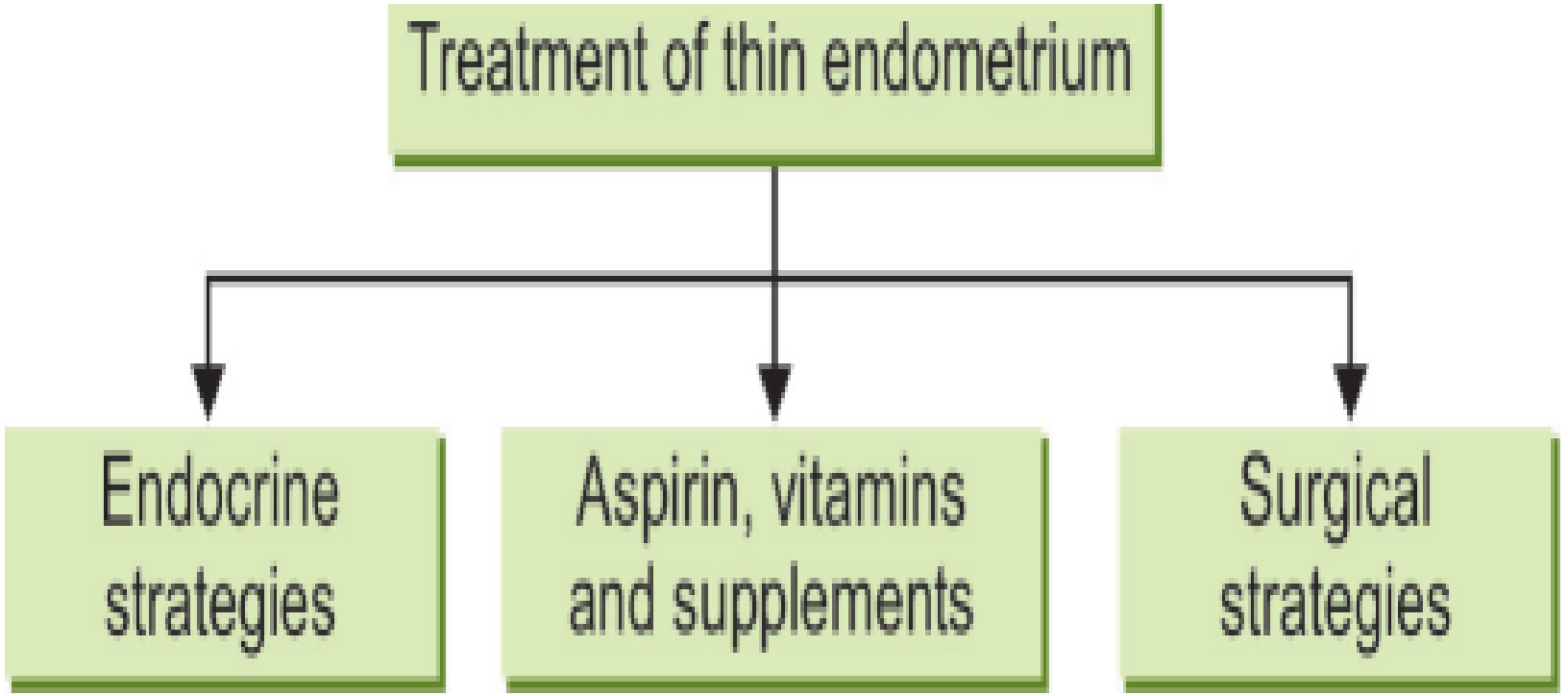
Synechiae Hysteroscopic adhesiolysis with hysteroscopic scissors

- **Repair** the **impaired lining**, ***restoring normal uterine cavity and fertility***

- Adhesiolysis permits the endometrium to ***re-establish its anatomy and function***, depending on the **degree** of the

- adhesions and the preoperative appearance of the endometrium observed with TVS.
- Much more than other conditions, IUAs are associated with a high **recurrence** rate **(3.1–62.5%),** which is dependent on **the severity** of adhesions

Treatment of Thin Endometrium



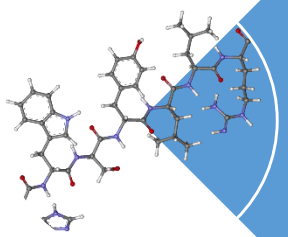
High dose oral estradiol Estrogen

- helps endometrial **proliferation** by causing **spiral artery contraction**
- and **reducing oxygen** tension in the **functional** layer, which facilitates
  - **embryo implantation**
- Different therapeutic approaches will most likely produce similar results, as exogenous estrogen administration compared with, or even combined with, endogenous estrogenic action from gonadotrophin administration **has not shown any superiority**

- استروژن برون زا در مقایسه با ، عملکرد استروژنی درون زا از گنادوتروپین
- هیچ برتری نشان نداده است

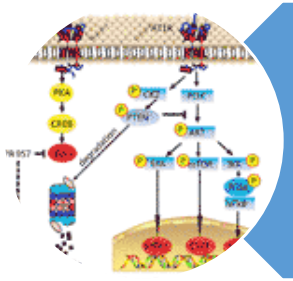
Intramuscular/transdermal/vaginal estradiol

- • Avoids first **liver** pass metabolism
- • Higher serum E2 concentrations Better **safety profile and**
- **longer** mean t½ Especially useful, when **treating high risk**
- patients, e.g. **advanced maternal age**
- No clear benefit for one over another, and have achieved similar pregnancy rates



GnRHa in luteal phase

- Improved **implantation and pregnancy** rate, by supporting the
- ***corpus luteum*** Luteal phase GnRHa (***triptorelin 0.1 mg on the day***
- ***of OPU, ET and 3 days later***) resulted in better pregnancy rate when
- compared with conventional luteal phase support. However the quality of evidence in low



Intrauterine G-CSF

- G-CSF increases **endometrial stromal cell decidualization**

mediated through **cAMP** by apocrine and paracrine action, and by

inducing proliferation and differentiation of the human Endometrium

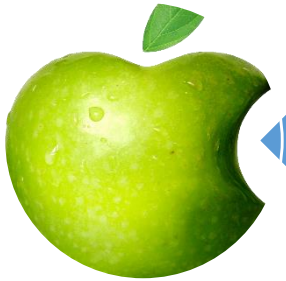
Autologous platelet rich plasma

- Activates platelets **by clotting, releases cytokines and growth factors**, including **VEGF, transforming growth factor, platelet-derived growth factor** and epidermal growth factor

- Five patients with refractory endometrium received **intrauterine PRP**, along with high dose estradiol valerate.

- All five patients achieved endometrial thickness >7 mm, and they were all pregnant after embryo transfer (4 ongoing pregnancy and 1 miscarriage).

- However **no other study has validated** these findings



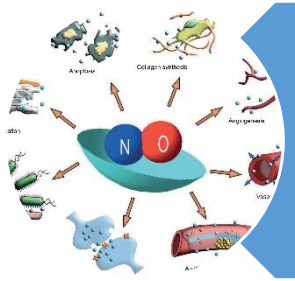
Treatment of thin endometrium—with aspirin vitamins and supplements

Aspirin •

Decreasing subendometrial contractions

- Inhibiting cyclo-oxygenase and prostaglandin biosynthesis
- Improving uterine endometrial blood flow

No beneficial effect on embryo implantation



Nitroglycerine patches Nitric oxide (NO)

- is involved in endometrial cycle control and uterine preparation for pregnancy.
- Drugs that release NO act as **vasodilating agenxZts**, so they might be useful in women with thin endometrium.
- Ohl et al. (2002) administered nitroglycerin **patches** the day **before embryo transfer** in women with repeated implantation failure, but these authors were unable to demonstrate any effect.
- There **is no current** evidence to support the use of nitroglycerin patches in women with a thin endometrium

Vitamin E + pentoxifylline

Vitamin **E—antioxidant and** vasodilatory effect

Pentoxifylline—inhibits phosphodiesterase by increasing intracellular

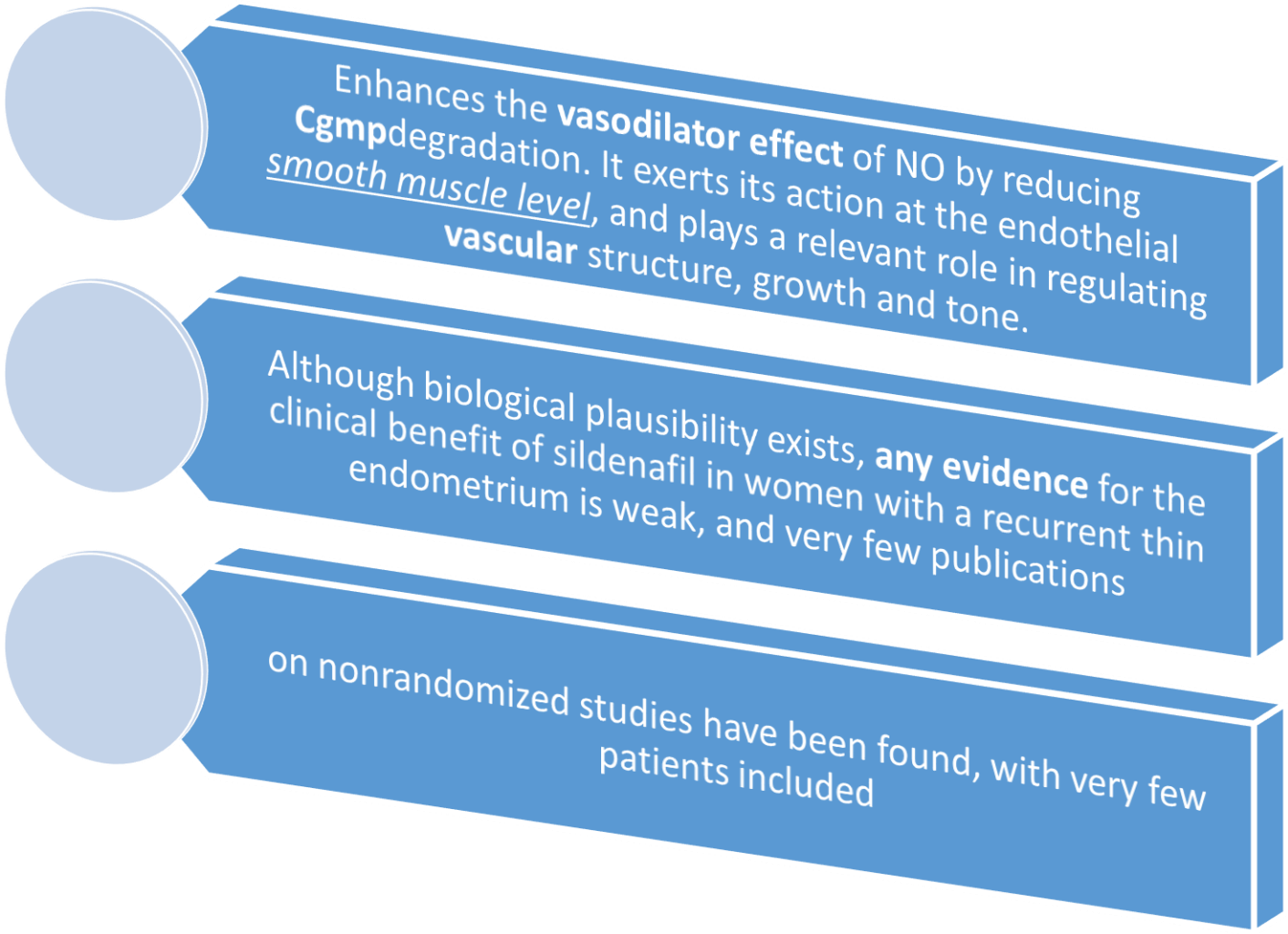
cAMP—has a vasodilating effect and ***increases red cell membrane***

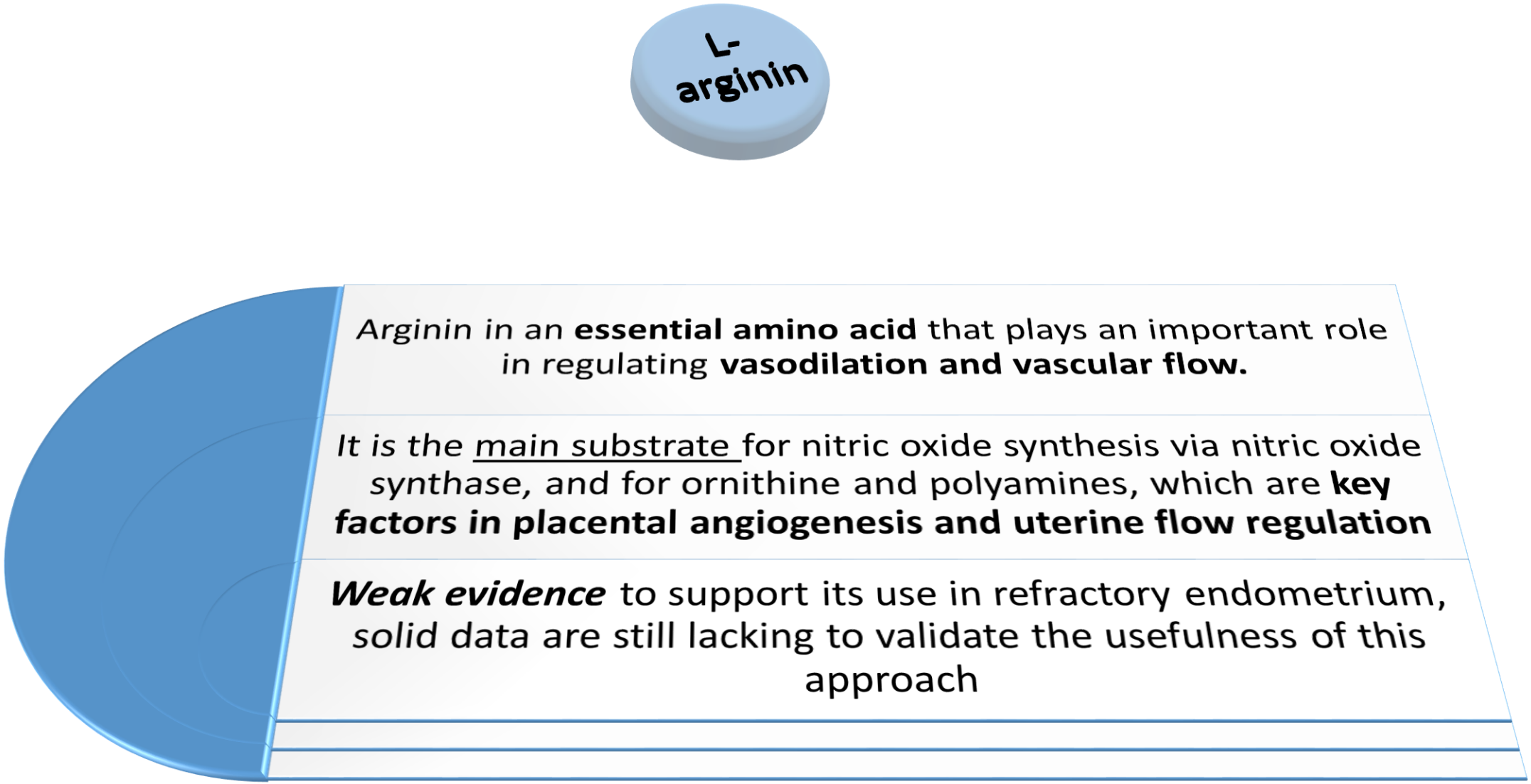
flexibility, while ***reducing blood viscosity*** by **inhibiting red cell**

aggregation Currently only observational studies,

no RCTs available

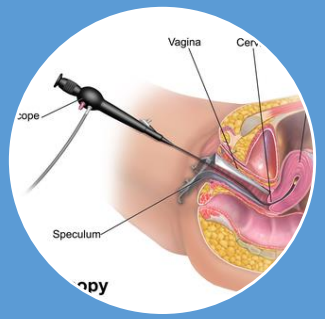
Sildenafil citrate



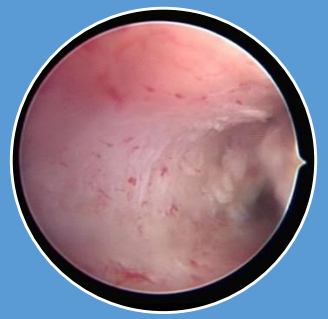

L-arginin
Arginin in an essential amino acid that plays an important role in regulating vasodilation and vascular flow.
It is the main substrate for nitric oxide synthesis via nitric oxide synthase, and for ornithine and polyamines, which are key factors in placental angiogenesis and uterine flow regulation
Weak evidence to support its use in refractory endometrium, solid data are still lacking to validate the usefulness of this approach

Treatment of thin endometrium—surgical strategy

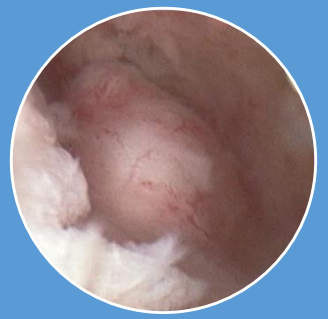
Hysteroscopy



Possible use could be to ***diagnose a previously unrecognized uterine*** pathology

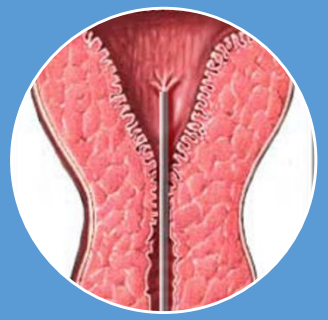


Hysteroscopy in the preceding cycle has been reported to improve **pregnancy outcomes** in couples with three or more failed ET cycles,



but this evidence has recently been contradicted by a multicenter, randomized controlled trial that showed hysteroscopy to be *of no value in RIF*

Endometrial scratch

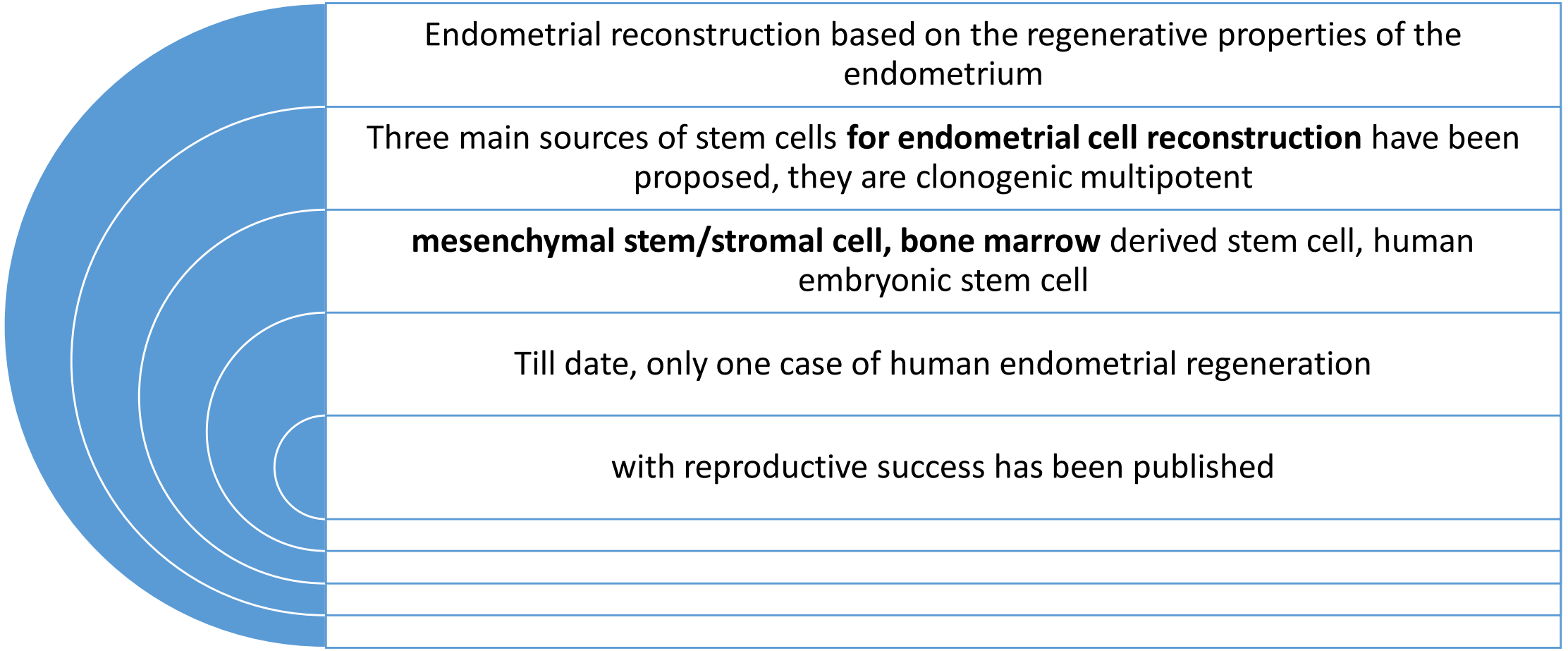


The healing process following endometrial scratch may release cytokines and growth factors which encourages endometrial growthand facilitates implantation

Meta-analysis including 14 trials and a total of 1,063 women concluded that moderate-quality evidence suggests that if 26% of women achieve live birth without endometrial injury, between **28% and 48% will achieve live birth with endometrial injury.**

A sensitivity analysis removing the studies at high risk of bias showed **no difference in effect**

Stem cells


Endometrial reconstruction based on the regenerative properties of the endometrium
Three main sources of stem cells **for endometrial cell reconstruction** have been proposed, they are clonogenic multipotent
mesenchymal stem/stromal cell, bone marrow derived stem cell, human embryonic stem cell
Till date, only one case of human endometrial regeneration
with reproductive success has been published

Uterine transplantation

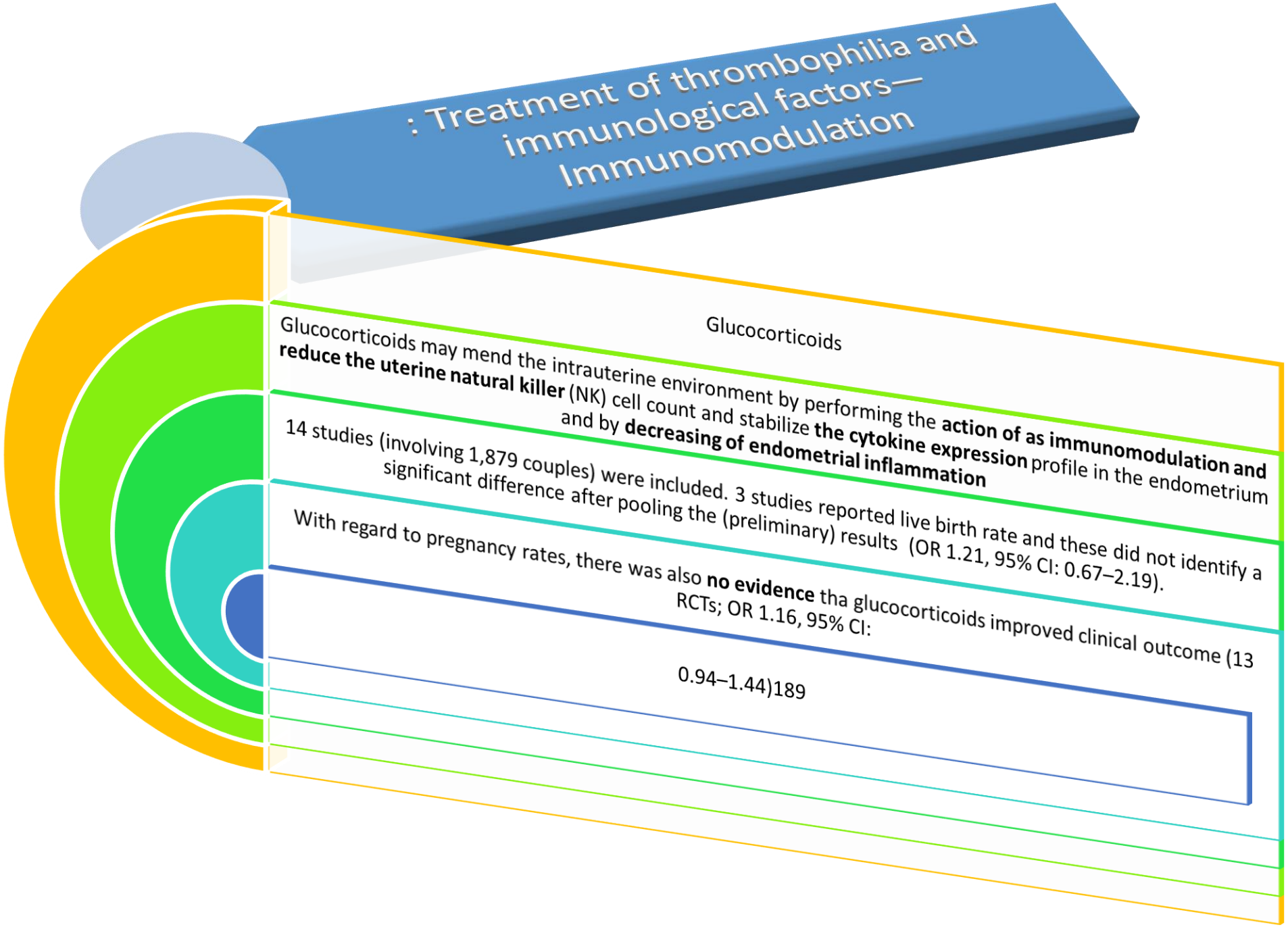
New therapeutic approach for women with absolute uterine factor infertility **(AUFI)**, in whom adoption or surrogacy is not acceptable

The first case of a healthy live birth after uterus transplantation

was published in 2014 in **one of the nine** women transplanted in

Sweden (Brännström et al., 2014)

Uterine transplantation as a promising clinical option for AUFI in the near future once experienced groups have settled the surgical, ethical and social matters related to this technique


: Treatment of thrombophilia and immunological factors— Immunomodulation
Glucocorticoids
Glucocorticoids may mend the intrauterine environment by performing the **action of as immunomodulation and reduce the uterine natural killer** (NK) cell count and stabilize **the cytokine expression** profile in the endometrium and by **decreasing of endometrial inflammation**
14 studies (involving 1,879 couples) were included. 3 studies reported live birth rate and these did not identify a significant difference after pooling the (preliminary) results (OR 1.21, 95% CI: 0.67–2.19).
With regard to pregnancy rates, there was also **no evidence** tha glucocorticoids improved clinical outcome (13 RCTs; OR 1.16, 95% CI:
0.94–1.44)189

Aspirin


Reduction of inflammation in the uterine cavity and improvement of uterine and ovarian perfusion, which might improve endometrial receptivity and ovarian responsiveness
13 trials (involving 2,653 couples) were included.
There was no evidence of a difference between the aspirin group and the group receiving no treatment or placebo in rates oflive birth (RR 0.91, 95% CI: 0.72–1.15, 3 RCTs, n = 1,053, I² = 15%, moderate-quality evidence).

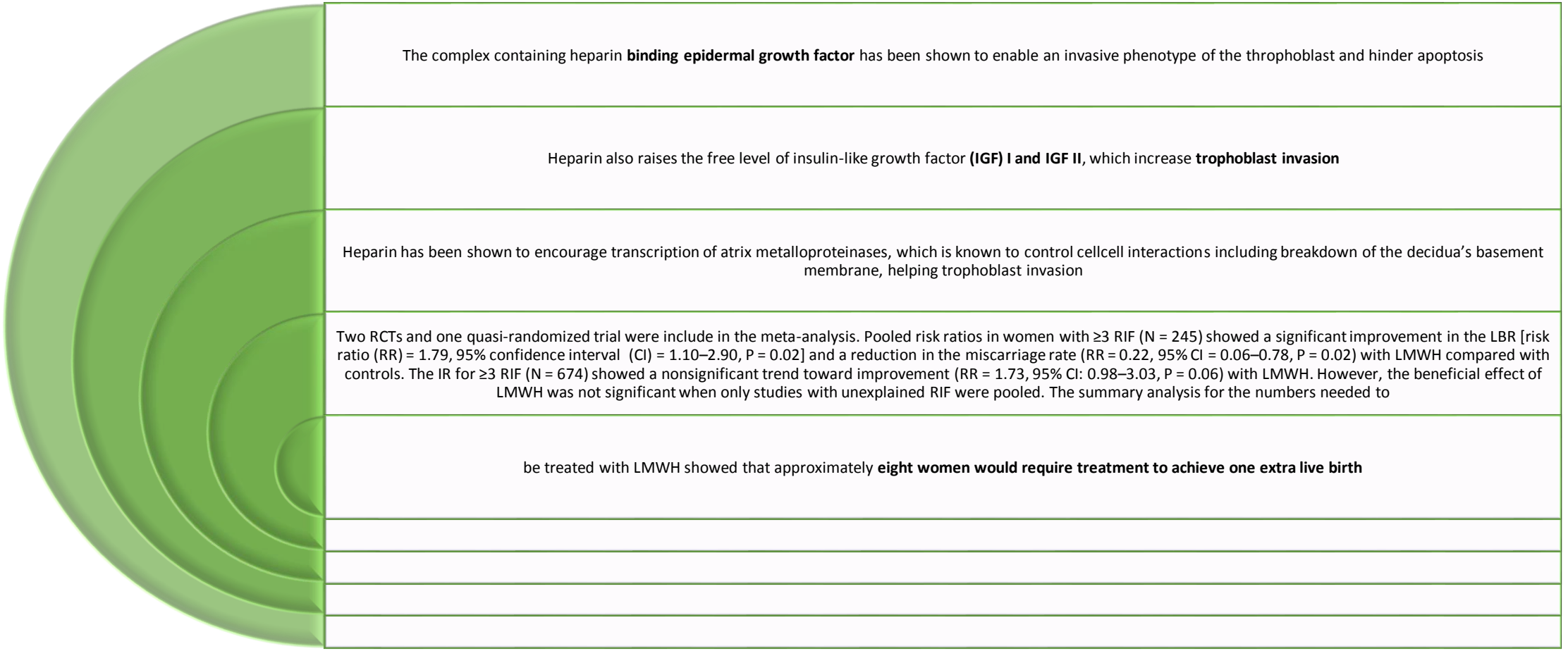
In addition, clinical pregnancy rates were also similar for the two groups (RR 1.03, 95% CI: 0.91–1.17, 10 RCTs, n = 2142, I^2 = 27%,

moderate-quality evidence).

There was no evidence of a difference between groups in terms of multiple pregnancy, miscarriage, ectopic pregnancy or vaginal bleeding.

Datawere lacking on other adverse effects

Heparin


The complex containing heparin **binding epidermal growth factor** has been shown to enable an invasive phenotype of the throphoblast and hinder apoptosis
Heparin also raises the free level of insulin-like growth factor **(IGF) I and IGF II**, which increase **trophoblast invasion**
Heparin has been shown to encourage transcription of atrix metalloproteinases, which is known to control cellcell interactions including breakdown of the decidua's basement membrane, helping trophoblast invasion
Two RCTs and one quasi-randomized trial were include in the meta-analysis. Pooled risk ratios in women with ≥3 RIF (N = 245) showed a significant improvement in the LBR [risk ratio (RR) = 1.79, 95% confidence interval (CI) = 1.10–2.90, P = 0.02] and a reduction in the miscarriage rate (RR = 0.22, 95% CI = 0.06–0.78, P = 0.02) with LMWH compared with controls. The IR for ≥3 RIF (N = 674) showed a nonsignificant trend toward improvement (RR = 1.73, 95% CI: 0.98–3.03, P = 0.06) with LMWH. However, the beneficial effect of LMWH was not significant when only studies with unexplained RIF were pooled. The summary analysis for the numbers needed to
be treated with LMWH showed that approximately **eight women would require treatment to achieve one extra live birth**

Intravenous immunoglobulin G (IVIG)

In ART, the proposed mechanism of action is by a **reduction of peripheral cytotoxic NK cells,**

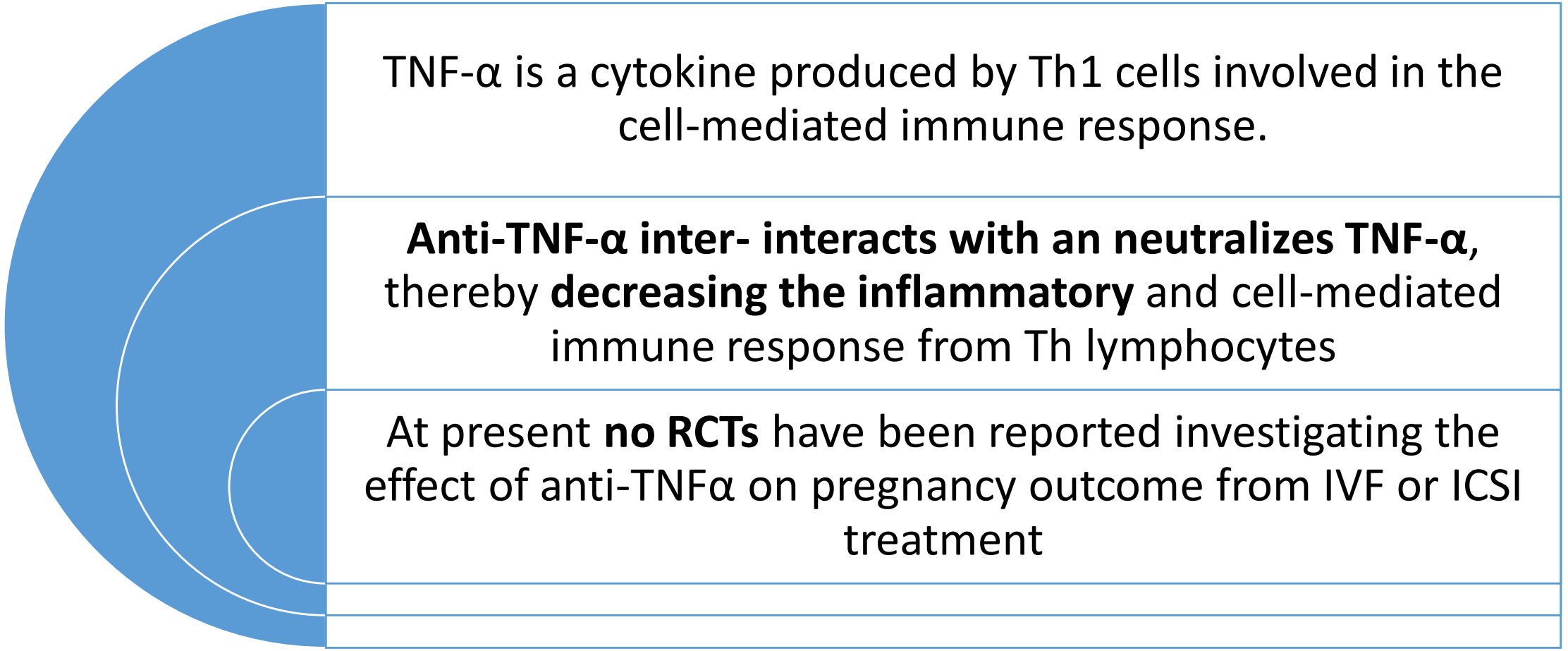
enhancement of regulatory T cells, and **downregulation of antibody producing B cells**

10 studies were included. The use of IVIG was **significantly associated with a higher implantation rate and RR was 2.708** (95% CI: 1.302–5.629) compared with the placebo.

The ***clinical pregnancy rate and the live birth rate*** were significantly increased in patients randomized to IVIG; RR was 1.475 (95% CI: 1.191–1.825) for the clinical pregnancy rate and RR was 1.616 (95% CI: 1.243–2.101) for the live birth rate.

Moreover, the **miscarriage rate was significantly less in** patients randomized to IVIG (0.352, 95% CI: 0.168–0.738**), but the live birth rate per embryo transferred was not (2.893; 95% CI: 0.810–10.331) less**.

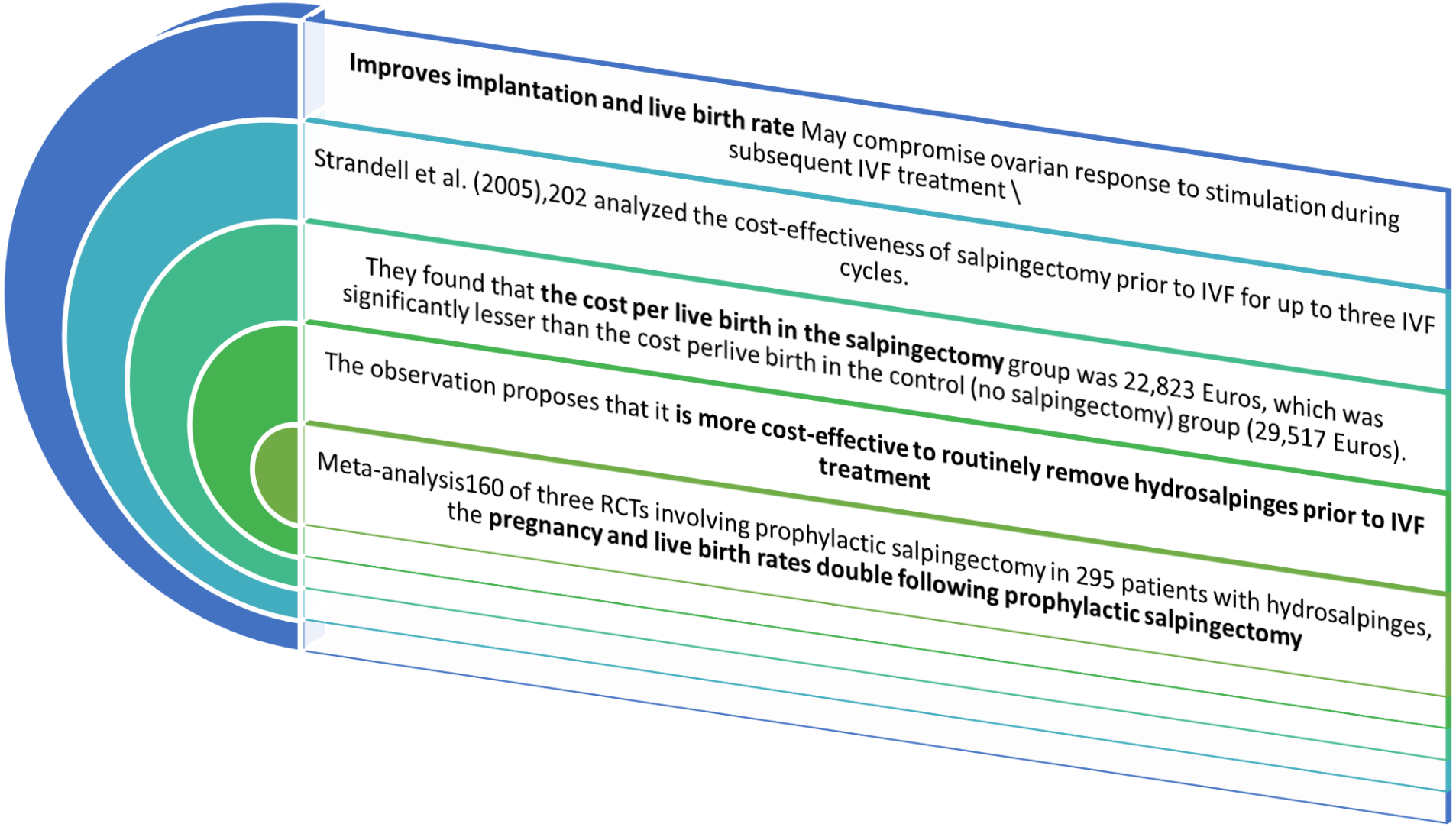
Anti-TNF-α


TNF-α is a cytokine produced by Th1 cells involved in the cell-mediated immune response.
Anti-TNF-α inter- interacts with an neutralizes TNF-α, thereby **decreasing the inflammatory** and cell-mediated immune response from Th lymphocytes
At present **no RCTs** have been reported investigating the effect of anti-TNFα on pregnancy outcome from IVF or ICSI treatment

Intralipid

- The therapeutic effect in the framework of IVF is proposed to be mediated by a **decrease of peripheral blood NK** cell activity and **suppression of proinflammatory cytokines**
- Only 1 RCT is available on this topic
- . No difference in chemical pregnancy was found between the two groups.
- The authors reported a borderline **significant difference in ongoing pregnancy and live birth in favor of intralipid,**
- but the study **was not sufficiently** powered to enable differentiation of this from a chance observation

Salpingectomy



Salpingostomy

- Salpingostomy not only “removes” the hydrosalpinges but also produces the possibility of natural Conception
- The **likely recurrence of hydrosalpinges after salpingostomy, which necessitates a further procedure to remove the tube,** further delaying the treatment and suffering extra cost The intrauterine pregnancy rate following salpingostomy has bee reported by a number of studies to be over **30%**
- The results are likely to be higher if the damage to the Fallopian tubes is minimal

Laparoscopic proximal tubal occlusion

- Simpler operation and less likely to *disturb ovarian blood supply* and hence compromise ovarian response to stimulation by gonadotrophins during IVF Treatment
- Occlusion of the **proximal part of the tube leaves** behind the dilated and blocked tube and increases the risk of future infection **(pyosalpinx**) and persistent pain which necessitates salpingectomy in future
- Meta-analysis206 by Johnson et al. (2010) provides evidence that laparoscopic tubal occlusion is an **alternative to** laparoscopic salpingectomy in improving IVF pregnancy rates in women with hydrosalpinges

USG-guided drainage of hydrosalpinx fluid