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GYNECOLOGICAL ENDOCRINOLOGY

THE 19TH WORLD CONGRESS

VIRTUAL CONGRESS

Ovarian failure - Biologic therapy

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BIOLOGIC THERAPY - definition

Cells - Autologous, allogenic, or xenogeneic **cells** propagated, expanded, selected, pharmacologically treated

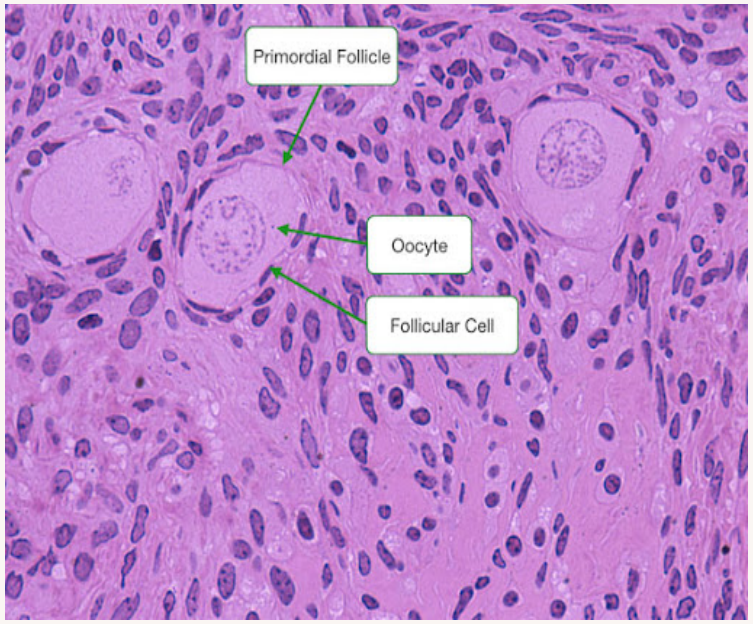
Cell products

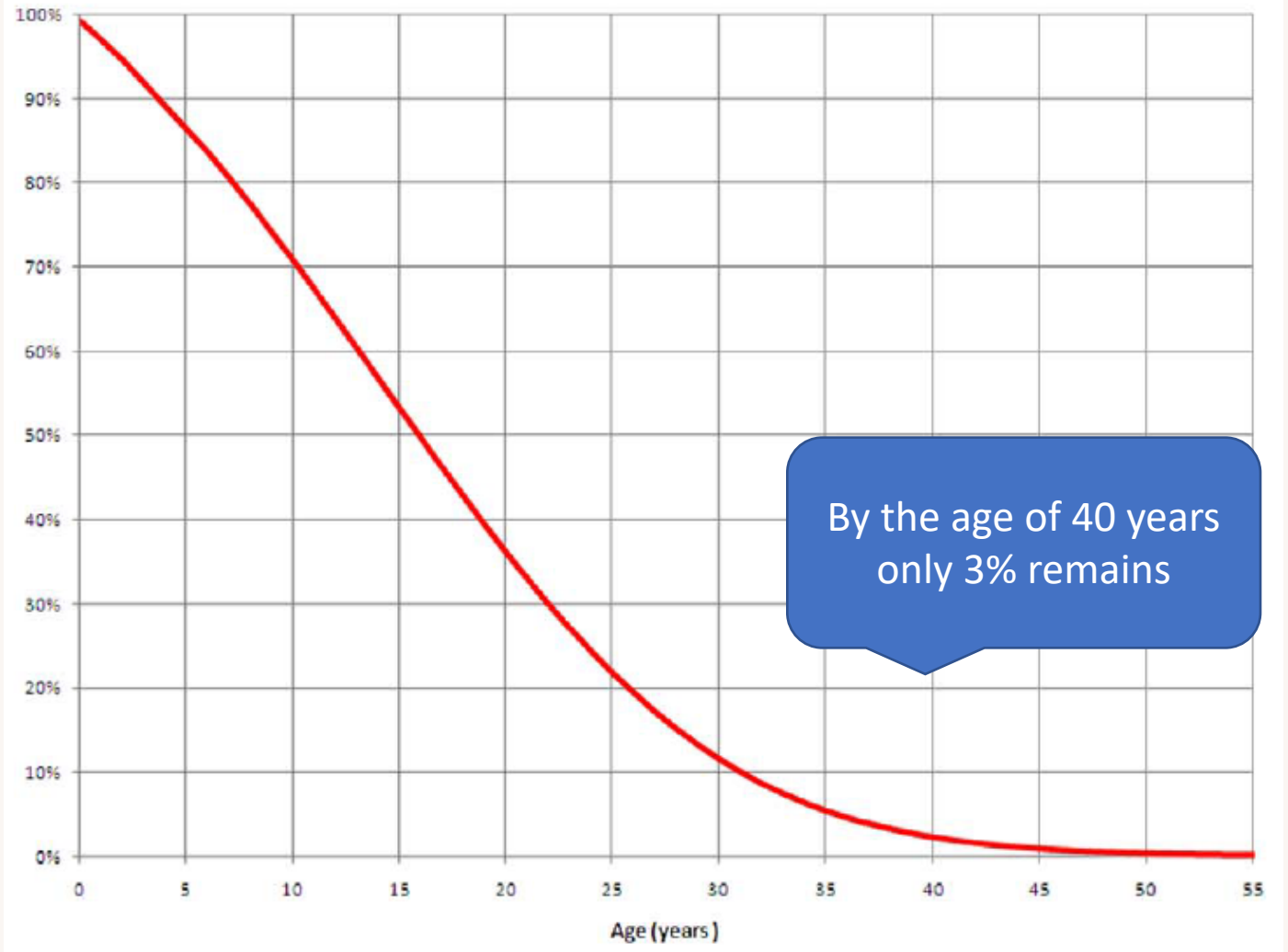
altered in biological characteristics *ex vivo* to be administered to humans

Prevention, treatment, cure, diagnosis or mitigation of **disease or injuries**

October 14, 1993. 58 FR 53248

BY *THE AGE OF 30* YEARS ONLY *12%* OF THE PRE-BIRTH PRIMORDIAL FOLLICLE POPULATION IS PRESENT





Walace and Kelsey, 2010

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THE MOST *CHALLENGING* PATIENTS IN ART

- Women of **advanced maternal age** with a low ovarian reserve make up 9%-24% of patients seeking ART.
- **Poor responders** with a low number of remaining antral, gonadotropin=dependant, stimulus responsive follicles within the ovaries.
- Women with **premature ovarian insufficiency** (POI) due to genetic, metabolic or autoimmune diseases, cancer treatment, idiopathic reasons etc.
  - Incidence of POI has been reported to be 1% in women younger than age 40 and 0.1% among women under 30 years.

THE *CONCEPT* OF OVARIAN REJUVENATION

- **Ovarian rejuvenation** is an attempt to overcome poor response by enhancing recruitment of resting follicles or improving quality og aging oocytes.

- It aims to **improve fertility** in women with **low ovarian reserve** due to **advanced maternal age** or **POI**
  - Three out of four women with POI have ovarian follicles remaining in the ovaries; yet, these follicles remain dormant (De Vos M et al., Lancet, 2010).

A NUMBER OF ALTERNATIVE OPTIONS ARE CURRENTLY BEING INVESTIGATED

- Intraovarian injection of Platelet Rich Plasma (PRP)
- Autologous Stem cell Ovarian Tranplatation (ASCOT)
- In Vitro Activation (IVA) of dormant follicles using chemical compounds and/or fragmentation
- SEGOVA – Combination (PRP+ASCOT+aIVA)
- Autologous mitochondrial transfer (AUGMENT) of oocytes

INTRAOVARIAN INJECTION OF PLATELET RICH PLASMA (PRP)

WHAT IS *PLATELET RICH PLASMA* (PRP) AND HOW IS IT *ADMINISTRED* FOR OVARIAN REJUVENATION

- ***Platelet Rich Plasma (PRP)*** is a highly concentrated solution of plasma, prepared from the patient`s own blood.
  - Contains a concentrated source of growth factors, namely insulin-like growth factor 1 and 2 (IGF-1, IGF-2), fibroblast growth factor (FGF), epidermal growth factor (EGF), transforming growth factor beta (TGF-b), hormones and cytokines.
- ***Intraovarian administration of autologous PRP;*** transvaginal, ultrasound-guided, intramedullary injection in the subcortical layers.
  - No standard protocol – approximately 2-5 mL PRP in each ovary (injections at multiple sites and at least three punctures per ovary with a 17-gauge needle).

WHAT IS THE EVIDENCE?

- PRP is know for it`s regenerative and tissue healing abilities, however, the potential beneficial role in ovarian regeneration is **merely a hypothesis.**
- No **animal studies** on effect on ovarian function following PRP injection.
- In 2016, Pantos et al - A group of 8 infertile menopausal women (with amenorrhea of 12-96 months). In **40% - menstrual cycles were restored** within 1-3 months after the injection, **18.5% resuption of ovulation** cycles, 1-5 oocytes obtained from the IVF cycles (Pantos et al., Abstract, ESHRE 32nd Annual Meeting 2016).
- In 2018, Sills et al. Injection of activated PRP in 4 cases and observed **increased AMH** and significantly **decreased FSH** levels with at least **one embryo** obtained from the IVF cycles (Sils et al., Gynecol Endocriol, 2018).

AUTOLOGOUS STEM CELL OVARIAN TRANSPLANT*

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*OVARIAN INFUSION OF BONE MARROW DERIVED STEM CELLS

INTRAOVARIAN *INFUSION* OF BONE MARROW DERIVED *STEM CELLS*

- Bone marrow derived stem cells (BMDSC) represent a heterogeneous group of mononuclear cells with multi-differentiation potential that includes several hematopoetic, mesenchymal and endothelial stem/progenitor cells.
- BMDSC infusion promotes human and mouse follicular growth by incerasing ovarian vascularization, stromal cell proliferation, and reducing cell death (Herraiz et al., 2016).
- Long-term fertility rescue has been achieved in chemotherapy-induced mouse ovaries mimicking aging, POR or POI after infusion of adult stem cell from different origins.
- The ASCOT technique (Herraiz et al., 2018):
  - The Autologous Stem Cell Ovarian Transplant (ASCOT) procedure require isolation of BMDSC from peripheral blood by apheresis (or bone marrow biopsy).
  - The stem cells are infused into the ovarian artery by catheterism (or direct injection via laparoscopy, transvaginal ultrasound-guided injection, or a combination).

IN VITRO ACTIVATION (IVA) OF DORMANT FOLLICLES*

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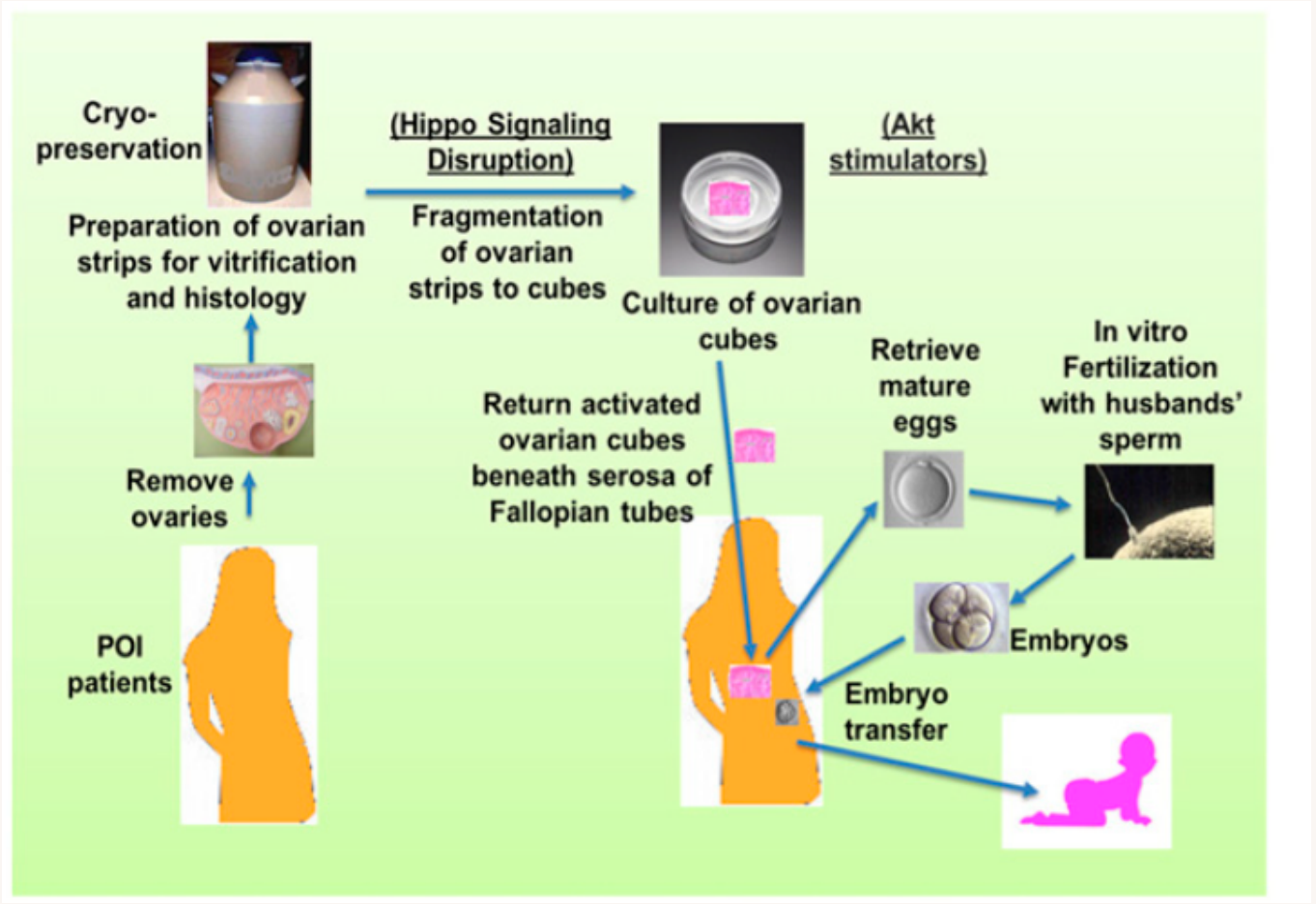
*USING CHEMICAL COMPOUNDS OR FRAGMENTATION

JAPAN 2013: *CLINICAL APPLICATION* OF IN VITRO ACTIVATION OF FOLLICLES IN *POI* PATIENTS



Kawamura et al., 2013

SEGOVA (PRP+ASCOT+aIVA)*

*USING AUTOLOGOUS COMPOUNDS AND FRAGMENTATION

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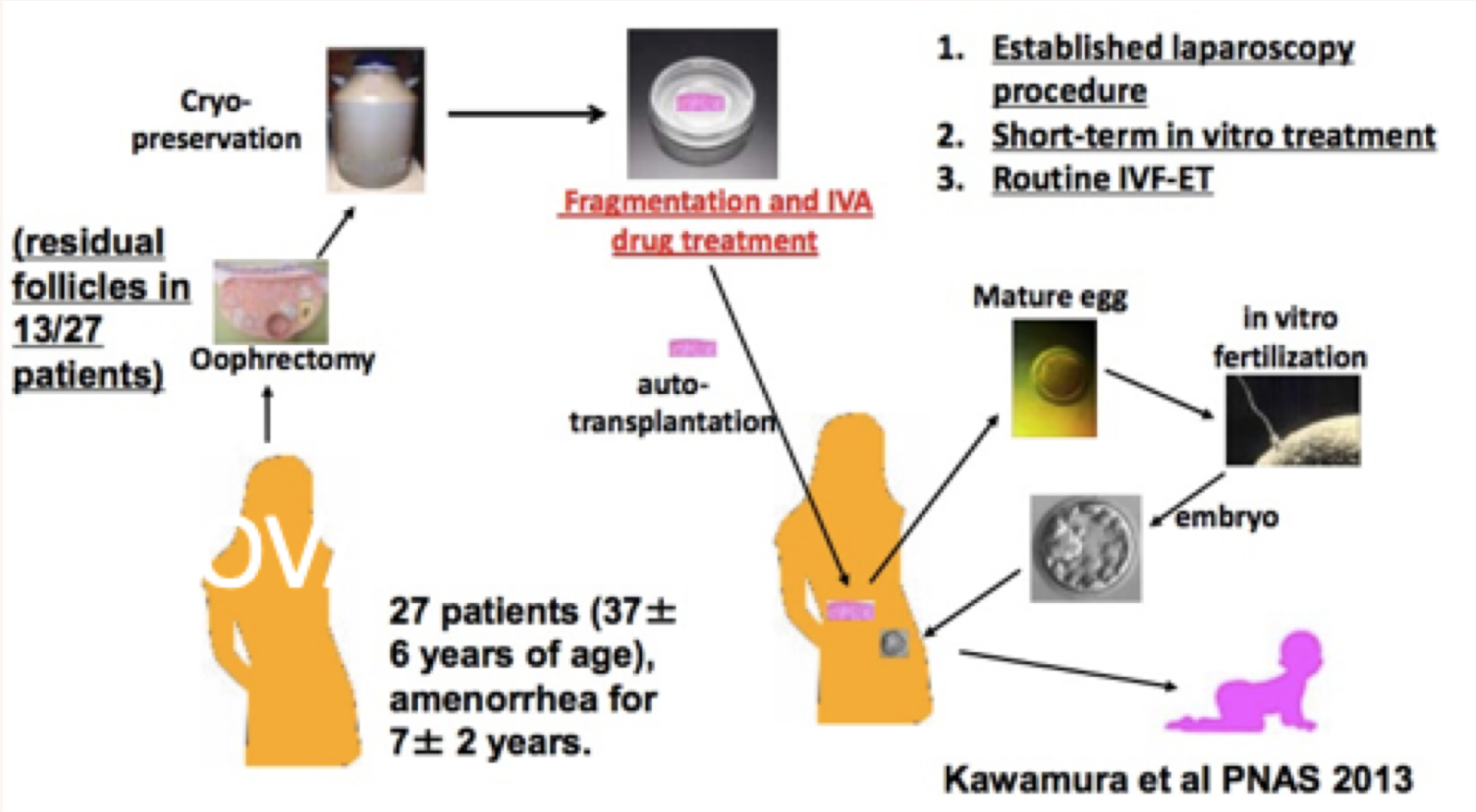
ClinicalTrials.gov Identifier: NCT04009473

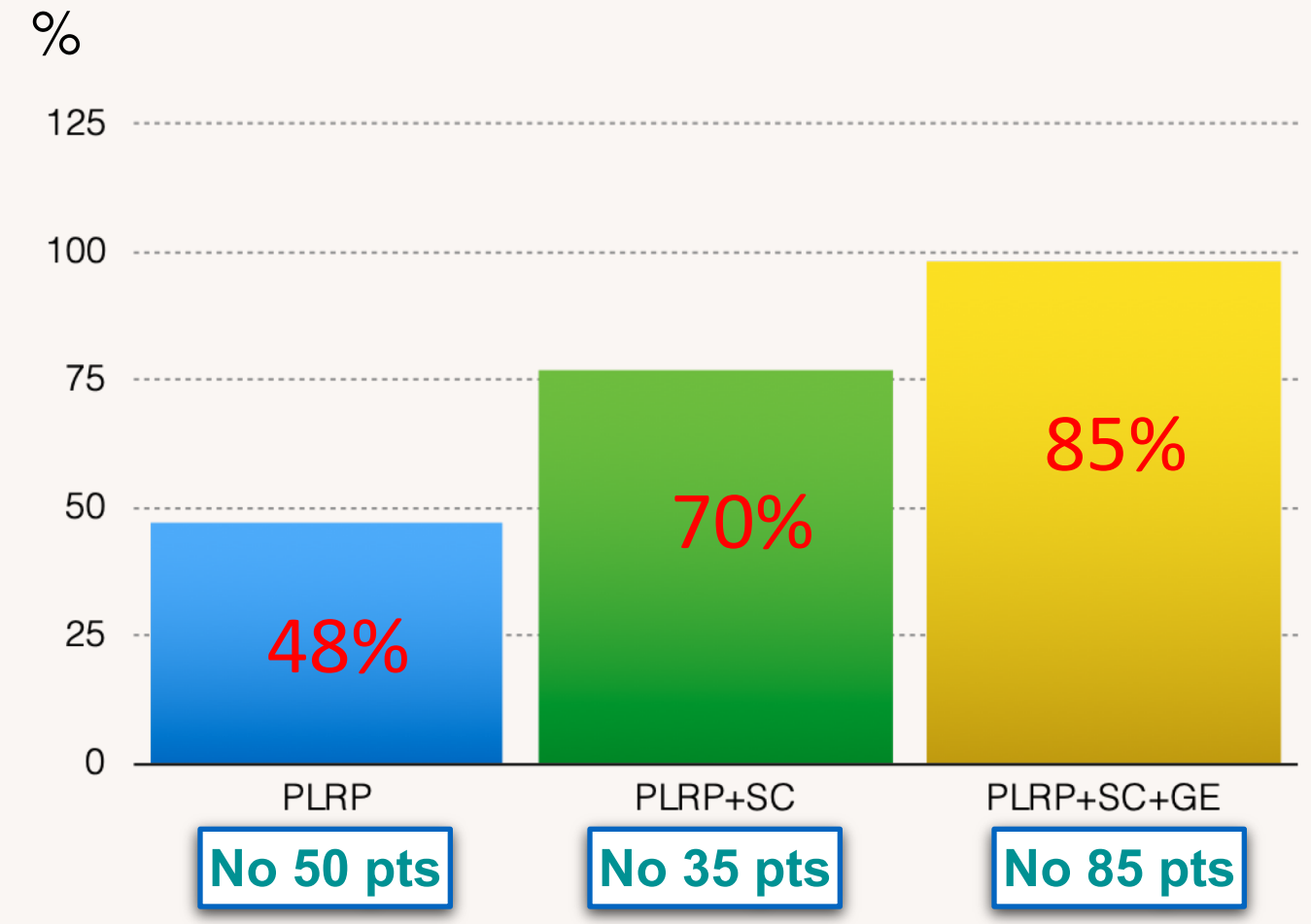
aIVA - Biologic therapy

Ovarian cortical biopsy
Microfragmentation
aPLRP incubation
US retransplantation



SEGOVA Hormones

The gonades regain their function



No 170 pts
2014-2019

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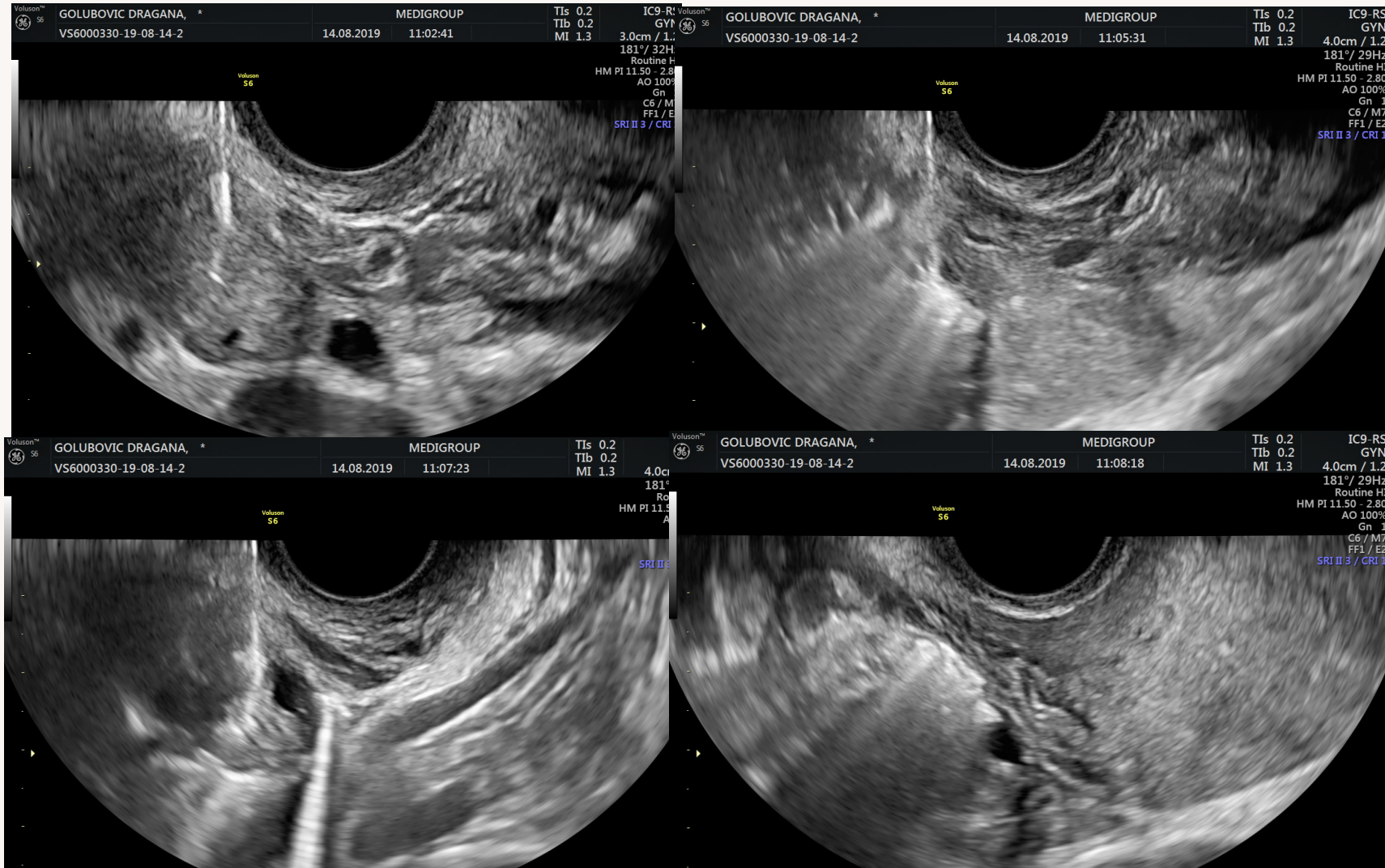
SEGOVA Outcome

- 85% Hormonal respond
- 10% Postmenopausal pregnancies



AUTOLOGOUS MITOCHONDRIAL TRANSFER IN CONNECTION WITH ICSI*

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*TO BOOST OOCYTE QUALITY IN „OLD“ OOCYTES

AUGMENT DID NOT SEEM TO IMPROVE PROGNOSIS AND THE STUDY WAS **DISCONTINUED**

CONCLUSION:

Injecting autologous mitochondria into the patient`s own oocyte at the time of ICSI **does not** benefit the developmental capacity of treated oocytes, the euploidy status of the embryo, nor the pregnancy rate.

The AUGMENT approach should not be considered as a novel way of ovarian rejuvenation in poor prognosis patients with a background of bad embryo quality.

TAKE HOME MESSAGES

- *intraovarian injection of Platelet-rich Plasma* (PRP) Clinical studies very limited and without proper controls the effect of the procedure in **inconclusive**.
- *Infusion of stem cells* (ASCOT) approach involving the whole BMDSC population seems to be a **promising approach** with a 33.3% treatment pregnancy rate.
- *In Vitro Activation* (IVA) of dormant follicles using chemical compounds and/or fragmentation appears to have a **low success rate** and studies are difficult to reproduce.
- *SEGOVA* (PRP+ASCOT+aIVA) of dormant follicles using autologous PRP compounds and/or fragmentation appears to increase **success rate** and studies are difficult to reproduce.
- Autologous *mitochondrial transfer* (AUGMENT) of oocytes in connection with ICSI **does not** seem to improve reproductive outcomes in poor-prognosis patients.