Ovarian Rejuvenation and Transvaginal Hydro Laparoscopy: An Added Value for Patients with Premature Ovarian Failure

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Posted Date: 9 August 2024

doi: 10.20944/preprints202408.0635.v1

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Article

Ovarian Rejuvenation and Transvaginal Hydro Laparoscopy: An Added Value for Patients with Premature Ovarian Failure

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Abstract: The term ovarian rejuvenation is used for treatments aiming to reactivate ovarian function in women suffering from premature ovarian insufficiency or women with poor ovarian response following ovarian stimulation treatments. Following Bologna criteria, patients with poor ovarian response (POR) are those patients with at least one previous stimulated cycle with POR, are of advanced maternal age, and have an abnormal ovarian reserve. Patients with at least 3 failed IVF cycles due to poor ovarian response (POR) and patients with POF with amenorrhea for at least 6 months, low estradiol, and high concentrations of LH and FSH were referred for ovarian PRP treatment. Out of 190 procedures, 15 were performed using the THL as there was an inaccurate visibility by vaginal ultrasound. Under direct visualization, PRP was injected in each ovary using a 19G needle. In the 53 patients referred for IVF, an embryo transfer was possible in 40% of the started cycles (n=21); the pregnancy rate per transfer was 52% with a live birth rate of 24%. The access to the pelvis by the THL enabled a direct visualization of both ovaries allowing a correct injection. Due to maternal age, patients should be informed of the elevated risks of 40% - 50% of biochemical pregnancies or miscarriages.

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Introduction

The term ovarian rejuvenation is used for treatments aiming to reactivate ovarian function in women suffering from premature ovarian insufficiency or women with poor ovarian response following ovarian stimulation treatments. Primary ovarian insufficiency (POI)or primary ovarian failure (POF) is a condition defined by the loss of normal ovarian function before the age of 40. Women diagnosed with POI suffer from oligo-amenorrhea, hot flushes, and conception problems. Various studies report that 1% - 3.7% of women suffer from POI (Lagergren et al., 2018, Rudnicka et al., 2018). It can be due to genetic factors (Turner, Fragile X, galactosemia). Still, etiology encompasses other multifactorial factors like immunological, environmental, smoking, and iatrogenic treatments like chemotherapy, radiotherapy, and extensive pelvic surgery. Nevertheless, in a majority of cases, the etiology remains unknown (Vabre et al., 2017). The diagnostic criteria following ESHRE guidelines are oligo/amenorrhea for at least 4 months and 2 consecutive FSH>25IU/L with a 4-week interval before the age of 40 (Webber et al., 2016). Following Bologna criteria, patients with poor ovarian response (POR) are those patients with at least one previous stimulated cycle with POR, are of advanced maternal age, and have an abnormal ovarian reserve (Ferraretti et al., 2011). The incidence of poor ovarian response is 25–29 % in IVF cycles (Keay and Jenkins, 2005) and >50% in women aged > 40 years (Ferraretti et al., 2011, Keay and Jenkins, 2005). The regenerative capacity of PRP has been known for a long time and is used regularly in orthopedics and esthetic medicine (Leo et al., 2015). Recently the use of PRP has been described as one of the add-ons in fertility treatment in an attempt to induce ovarian reactivation(Pantos et al., 2019, Sharara et al., 2021, Sills and Wood, 2019). Animal studies showed a positive effect on ovarian function after the ovarian injection of PRP. After induction of POI by chemo toxic agents in rats, intra-ovarian PRP injection reduced the extent of follicular atresia and inflammatory responses with a decreased

 doi:10.20944/preprints202408.0635.v1

concentration of FSH after 8 weeks (Ahmadian et al., 2020, Dehghani et al., 2018). Intra-ovarian injection of PRP in cows with hypoovarian function resulted in the normalization of ovulatory function and increasing numbers of harvested oocytes (Cremonesi et al., 2020). PRP has a 3-5-fold higher concentration of platelets compared to peripheral blood and a 5-10-fold higher concentration of growth hormones (Sharara et al., 2021). Routinely intra-ovarian application of the PRP is done transvaginal under ultrasound guidance. In patients with POR ovaries are mostly clearly visible under ultrasound and injection can easily be performed. In patients with POF with amenorrhea of at least 6 months, ovaries are small without the presence of antral follicles, and as such identification by ultrasound can be challenging. To avoid incorrect application, we decided to perform the intra-ovarian injection of PRP in these patients using the technique of transvaginal hydro-laparoscopy (THL) enabling injection under direct endoscopic visualization.

Materials and Methods

Patients with at least 3 failed IVF cycles due to poor ovarian response (POR) and patients with POF with amenorrhea for at least 6 months, low estradiol, and high concentrations of LH and FSH were referred for ovarian PRP treatment. After collecting 60 ml of blood, the sample is centrifuged for 4 min at 3200 revolutions per minute in a special vial (Figure 2). The final concentration of platelets is 600000-700000/ µl. Using a 19G needle 3ml of PRP is injected through a single injection place into each ovary under ultrasound guidance or in the case of POF access to the pelvis is gained by THL. All the procedures are performed under conscious sedation in a day hospital setting. A second PRP application is performed 4-6 weeks later.

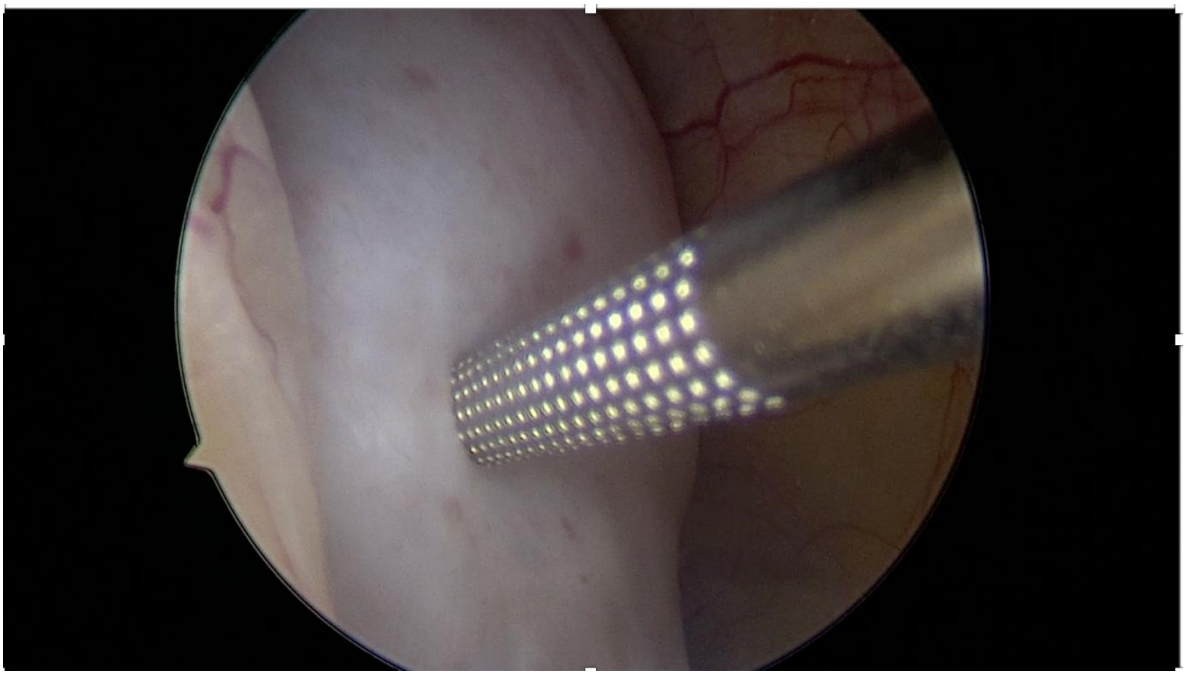

Figure 2. Visualization of the ovary and injection needle in a patient with POF.

Technique

The technique of THL is based upon a simple needle puncture technique of the posterior fornix using a spring-loaded needle with a soft transition from the needle diameter to the diameter of the outer trocar, enabling the endoscope's insertion (Figure 1). The technique is extensively described in previous publications (Campo et al., 1999, Gordts et al., 2000, Gordts et al., 1998, Tros et al., 2020, Watrelot et al., 1999). It is an ambulatory procedure performed in a day hospital setting under conscious sedation. In a recent publication of 2288 THL procedures, the failure rate of access was 1% due to tenting of the peritoneum and the complication rate was 0.74%, in 4 patients due to small bleeding at the posterior leave of the broad ligament requiring a laparoscopy for non-complicated hemostasis with bipolar and in 13 patients due to a perforation of the rectum only requiring a

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conservative approach with 6 day of antibiotics. (Gordts et al., 2021). The rectal perforation rate in a much larger series of 13360 procedures was 0.37% (n=50). All patients were treated with antibiotics for 6 days, not requiring surgery (Gordts S et al., 2008). Most of these perforations are retro-peritoneal due to the presence of adhesions, are directly visualized and the lesion is maximal 4 mm.

Figure 1. (a) Mounted system of the springloaded needle with smooth dilatation of diameter needle till the diameter of the outer trocar. (b) 2.9 mm endoscope. (c) Obturator and trocar with operative channel.

All patients were informed that the treatment of ovarian PRP is still experimental and that up till now not enough data are known to predict a successful outcome; informed consent was given also for THL in case this has to be performed.

Results

Of the 190 procedures, 82 patients (mean age 39 ± 4) had enough follow-up to evaluate the live birth rate. We limited our data analysis to this group of patients as this is their final goal. 53 patients were referred for an IVF treatment and 29 were after discussion opting for a spontaneous evolution. Out of 190 procedures, 15 were performed using the THL as there was an inaccurate visibility by vaginal ultrasound. Under direct visualization, PRP was injected in each ovary using a 19G needle (Cook°).

Where initially 2 – 3 injection places were used as described in the literature, it became clear at THL that the PRP injected at the second or third injection place came out via the previous injection places. For this reason, we now limit the injection of PRP to one injection place. In contrast to patients with POR, the ovaries of POF patients are smaller, have mostly a more yellow aspect, and in the absence of visual antral follicles, consistency is harder and more fibrotic. As a consequence, puncturing of such a smaller and more fibrotic ovary and the presence of a watery distension medium used for the THL procedure, the ovaries tend to slide away and utmost attention must be paid to place the punction needle perpendicular to the ovarian surface avoiding the needle to slide away. It requires rotating the endoscope to obtain the correct positioning of the needle (Figure). There were

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no direct or late complications. The pregnancy rate in the group of patients with spontaneous evolution was 24% with a live birth rate of 14 %. In patients with POF, cycle recovery occurred in 35 % after 2-3 months. In the patients referred for IVF treatment, the mean number of oocytes was 3 (± 1,5); 40% of the started cycles resulted in an embryo transfer (n=21). The pregnancy rate per transfer was 52% with a live birth rate of 24%.

Discussion

In this small retrospective study, we examined the results of the intraovarian application of PRP. Although still experimental and without a control group, results must be interpreted carefully. Nevertheless, in our group of POR and POF patients intraovarian injection of PRP resulted in live births using autologous oocytes, where patients otherwise should have been referred to an oocyte donation program. Although patients previously were already treated with IVF, 29 couples with normal male fertility, opted for a spontaneous evolution, resulting in a 24 % pregnancy rate and a 14% live birth rate. In the 53 patients referred for IVF, an embryo transfer was possible in 40% of the started cycles (n=21); the pregnancy rate per transfer was 52% with a live birth rate of 24%. Due to maternal age, patients should be informed of the elevated risks of 40% - 50% of biochemical pregnancies or miscarriages.

The access to the pelvis by the THL enabled a direct visualization of both ovaries allowing a correct injection. As an added value it allows the inspection of the female pelvis whereby normal findings and in the absence of other fertility impairing factors a spontaneous evolution for 6-8 months can be discussed with the patients, referring to the spontaneous live birth rate of 14%. Based upon our endoscopic findings by direct visualization of the small size of the ovaries of POF patients, we opted for the use of a 19G needle (Cook°) instead of the 17G needle recommended in other publications. The smaller diameter of the 19G needle didn't provoke any difficulty in the injection of the viscous PRP solution. It became obvious that a single needle puncture place is advisable as we saw that in the case of 2-3 injection places, the injected PRP came out through the other puncture places. Reporting the number of puncture places in publications is therefor important as this could be an explanation why in some publications no positive effect was seen by the use of PRP in terms of implantation rates and clinical pregnancy rates.

References

Ahmadian S, Sheshpari S, Pazhang M, Bedate AM, Beheshti R, Abbasi MM, Nouri M, Rahbarghazi R, Mahdipour M. Intra-ovarian injection of platelet-rich plasma into ovarian tissue promoted rejuvenation in the rat model of premature ovarian insufficiency and restored ovulation rate via angiogenesis modulation. *Reprod Biol Endocrinol* 2020;18: 78.

Campo R, Gordts S, Rombauts L, Brosens I. Diagnostic accuracy of transvaginal hydrolaparoscopy in infertility. *Fertil Steril* 1999;71: 1157-1160.

Cremonesi F, Bonfanti S, Idda A, Anna LC. Improvement of Embryo Recovery in Holstein Cows Treated by Intra-Ovarian Platelet Rich Plasma before Superovulation. *Vet Sci* 2020;7.

Cremonesi F, Bonfanti S, Idda A, Lange-Consiglio A. Platelet Rich Plasma for Regenerative Medicine Treatment of Bovine Ovarian Hypofunction. *Front Vet Sci* 2020;7: 517.

Dehghani F, Aboutalebi H, Esmaeilpour T, Panjehshahin MR, Bordbar H. Effect of platelet-rich plasma (PRP) on ovarian structures in cyclophosphamide-induced ovarian failure in female rats: a stereological study. *Toxicol Mech Methods* 2018;28: 653-659.

Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L, Definition EwgoPOR. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Hum Reprod* 2011;26: 1616-1624.

Gordts S, Campo R., Puttemans P., Gordts Sy., I. B. Transvaginal access: a safe technique for tubo-ovarian exploration in infertility? Review of the literature. *Gyn Surg* 2008;5: 187-191.

Gordts S, Campo R, Brosens I. Office transvaginal hydrolaparoscopy for early diagnosis of pelvic endometriosis and adhesions. *J Am Assoc Gynecol Laparosc* 2000;7: 45-49.

Gordts S, Campo R, Rombauts L, Brosens I. Transvaginal hydrolaparoscopy as an outpatient procedure for infertility investigation. *Hum Reprod* 1998;13: 99-103.

 doi:10.20944/preprints202408.0635.v1

Gordts S, Gordts S, Puttemans P, Segaert I, Valkenburg M, Campo R. Systematic use of transvaginal hydrolaparoscopy as a minimally invasive procedure in the exploration of the infertile patient: results and reflections. *Facts Views Vis Obgyn* 2021;13: 131-140.

Keay SD, Jenkins JM. Predictive value of poor ovarian response to initial gonadotropin stimulation. *Fertil Steril* 2005;84: 1797; author reply 1797-1798.

Lagergren K, Hammar M, Nedstrand E, Bladh M, Sydsjö G. The prevalence of primary ovarian insufficiency in Sweden; a national register study. *BMC Womens Health* 2018;18: 175.

Leo MS, Kumar AS, Kirit R, Konathan R, Sivamani RK. Systematic review of the use of platelet-rich plasma in aesthetic dermatology. *J Cosmet Dermatol* 2015;14: 315-323.

Pantos K, Simopoulou M, Pantou A, Rapani A, Tsioulou P, Nitsos N, Syrkos S, Pappas A, Koutsilieris M, Sfakianoudis K. A Case Series on Natural Conceptions Resulting in Ongoing Pregnancies in Menopausal and Prematurely Menopausal Women Following Platelet-Rich Plasma Treatment. *Cell Transplant* 2019;28: 1333-1340.

Rudnicka E, Kruszewska J, Klicka K, Kowalczyk J, Grymowicz M, Skórska J, Pięta W, Smolarczyk R. Premature ovarian insufficiency - aetiopathology, epidemiology, and diagnostic evaluation. *Prz Menopauzalny* 2018;17: 105-108.

S. G. Transvaginal access: a safe technique for tubo-ovarian exploration in infertility? Review of the literature. In R. C (ed). 2008. Springer, Gynecol Surg pp. 187 – 191.

Sharara FI, Lelea LL, Rahman S, Klebanoff JS, Moawad GN. A narrative review of platelet-rich plasma (PRP) in reproductive medicine. *J Assist Reprod Genet* 2021;38: 1003-1012.

Sills ES, Wood SH. Autologous activated platelet-rich plasma injection into adult human ovary tissue: molecular mechanism, analysis, and discussion of reproductive response. *Biosci Rep* 2019;39.

Tros R, van Kessel M, Oosterhuis J, Kuchenbecker W, Bongers M, Mol BW, Koks C. Transvaginal hydrolaparoscopy and laparoscopy. *Reprod Biomed Online* 2020;40: 105-112.

Vabre P, Gatimel N, Moreau J, Gayrard V, Picard-Hagen N, Parinaud J, Leandri RD. Environmental pollutants, a possible etiology for premature ovarian insufficiency: a narrative review of animal and human data. *Environ Health* 2017;16: 37.

Watrelot A, Dreyfus JM, Andine JP. Evaluation of the performance of fertiloscopy in 160 consecutive infertile patients with no obvious pathology. *Hum Reprod* 1999;14: 707-711.

Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, Cifkova R, de Muinck Keizer-Schrama S, Hogervorst E, Janse F *et al.* ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod* 2016;31: 926-937.