

# Efforts to optimize in vitro fertilisation protocols

PhD Theses

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During the 20th century a number of medical discoveries have been made that have a tremendous effect of the everyday life of the average people (in addition to their scientific merits). These include the development of assisted reproduction therapies that provide a hope for infertile couples.

During the past two decades the age when women give birth to their first child increased significantly due to a number of socio-economic factors. One of the major drawbacks of this tendency is that the fertility of an older woman is impaired. In addition, older women's often have an older partner whose fertility may be also frequently impaired. Consequently, the number of pairs requiring assisted reproduction therapies is dramatically increasing.

According to an old 'bon mot' a woman is able to do almost everything for two things: to have a child and to not have a child. As an expert of assisted reproduction therapies I can fully reinforce this experience.

When at 1st March, 1999 I first entered to the Outpatient Clinic of Fertility at Szent Janos Hospital, my first observation was the crowded room full with heterogeneous pairs; some of them just learned the success of the intervention, while others faced with the fail of the therapy. This scene is still present for me as it clearly indicates how close are the success and fails, happiness and sadness in this field of medicine.

My task is to increase the rate of successful interventions of assisted reproduction therapies. During my professional career I should regularly up-date my knowledge with latest advances in the field and to transfer them to the practice as soon as possible. During my Theses I summarize my experience related with this work.

## AIMS

ART including IVF is a dynamically developing science. Therefore when I first participated in the therapy of infertile women in 1st March, 1999, the therapeutic and diagnostic arsenal available at that time differed significantly from those available nowadays. In addition, the safety and efficacy of some of the regimes used nowadays routinely were also not assessed that time.

The aim of my PhD work was to clarify some practical questions affecting the technique and success of IVF in the following areas.

- A. Are the results in term of pregnancy rates obtained with GnRH antagonist protocol comparable to those with GnRH agonist long protocol during IVF?
- B. Is the pregnancy rate with IVF treatment altered if recombinant hCG is given instead of urinary hCG?
- C. Which protocol for the pretreatment of endometry before the implantation of frozen-thawed embryo is the most effective approach in term of pregnancy rate?
- D. Does  $\beta$ -hCG values measured on day 14 after fertilization of oocyte have any predictive value during IVF therapy?
- E. What are the limitations of ultrasound when ectopic IVF-ET pregnancies are assessed?
- F. Is the risk of adnex torsion increased after an IVF-ET?

## **A Are the results in term of pregnancy rates obtained with GnRH antagonist protocol comparable to those with GnRH agonist long protocol during IVF?**

GnRH antagonist protocols have several advantages over the GnRH agonist long protocols. The administration of GnRH antagonists is substantially shorter and simpler, less gonadotropin is required to reach controlled hyperstimulation of the ovaries (COH) and the risk of OHSS is also low. Further advantage is the maintained endogenous LH levels that allow to perform the stimulation with recFSH alone. In our Centre we are applying GnRH antagonist protocols for IVF since May, 2000. Analyzing the clinical data of patients treated in our Centre we analyzed whether the efficacy of GnRH antagonist protocols corresponds to that published by other institutes.

### **Patients and methods\***

We retrospectively analyzed the data of IVF cycles performed between 1st July, 2004 and 28th, February, 2005 with the aim to compare the outcomes after IVF long protocols and the recently introduced antagonist protocols.

In case of IVF long protocols we started the s.c. administration of triptoreline, a GnRH analogue agonist (0.1 mg/day) in the midluteal phase, up to the required downregulation of hypophyseal receptor, then until the day of oocyte retrieval.

In case of antagonist protocols we started the s.c. administration of ganirelix, a GnRH antagonist on Day 5 of the cycle (0.25 mg/day) until the day of oocyte retrieval. COH was performed by the administration of recFSH and hMG in a ratio of 3:1. The dose of recFSH was based on patients' age, body mass index, basal FSH levels and ultrasound (US) findings of the ovaries. Oocyte retrievals were performed 35 hours later. Oocytes were fertilized with IVF techniques or, in case of specific sperm characteristics, with ICSI techniques. Luteal phase was supported with intravaginally administered micronized progesterone (P).

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\* All studies performed within the frame of my PhD work were approved by the competent Institutional Ethical Committee.

## Results

The results are summarized in Table 1.

	<b>Antagonist protocol</b>	<b>Long protocol</b>	<b>Level of significance</b>
Number of treated patients	136	314	
Age (year)	32.6 ± 4.2	31.4 ± 4.0	p<0.05
BMI (kg/m <sup>2</sup> )	22.4 ± 3.1	22.8 ± 3.4	ns
Basal FSH (IU/L)	6.7 ± 1.8	6.4 ± 1.6	ns
Serum E2 level on day of hCG administration (pg/ml)	2232 ± 926	2757 ± 816	p<0.001
Endometrium thickness on the day of hCG administration (mm)	11.3 ± 1.6	12 ± 2	p<0.001
Amount of FSH-HMG used (NE)	1851 ± 917	2411 ± 1065	p<0.001
Number of metaphase II oocytes	6.5 ± 3.4	8 ± 3.0	p<0.001
Number of zygotes	5.1 ± 3.0	5.9 ± 2.7	p<0.01
Number of transferred embryos	2.45 ± 1.0	2.75 ± 0.8	p<0.01
Rate of ongoing pregnancies	29.8% (n = 37)	30.8% (n = 92)	ns
Rate of pathological pregnancies	16.9% (n = 23)	13.0% (n = 41)	ns
Rate of cancelled cycles	8.8% (n = 12)	4.8% (n = 15)	ns
Rate of severe OHSS	0.8% (n = 1)	1.6% (n = 5)	Ns

**Table 1.** Outcomes in patients treated with antagonist or long protocol (mean ± SD)

## **Discussion**

Our retrospective analysis demonstrated that during cycles of patients subjected to antagonist protocols the serum estradiol (E2) levels are significantly lower, and the number of mature follicles, MII oocytes and embryos available for embryo transfer (ET) are also lower compared to those subjected to agonist protocols. An explanation for the difference may be that the antagonist therapy is initiated on Day 2-3 of menstrual cycle, in that phase when the spontaneous follicular recruitment occurs in the presence of intact endogenous LH secretion. In spite of the differences observed in hormone levels our analysis indicates that the pregnancy outcomes after IVF with antagonist protocols are comparable to those after the 'gold standard' long protocols.

The benefits of GnRH antagonist protocols over GnRH agonist protocols include patients' better compliance to GnRH antagonists; the shorter duration of therapy; the lower prevalence of OHSS. In addition, lower gonadotropin doses are required. Based on comparable pregnancy results we concluded that GnRH antagonist protocols can be safely and effectively used for COH.

## **B. IS THE PREGNANCY RATE WITH IVF TREATMENT ALTERED IF RECOMBINANT HCG IS GIVEN INSTEAD OF URINARY HCG?**

A number of well designed randomized clinical studies (RCT) demonstrated the bioequivalence of urinary and recombinant hCG products (uhCG and rhCG, respectively). RCTs compare different treatment protocols under well controlled conditions in a highly selected patient population, therefore, the results obtained do not reflect necessarily the real life conditions (i.e. they are observer in a more heterogeneous population, without the absolute availability of monitoring tools, otherwise required for an RCT). Therefore, in addition to RCTs, further non-interventional (observational) studies are also needed to reinforce the comparable efficacy of rhCG and uhCG products.

### **Patients and methods\***

In our center colleagues performing IVF can freely decide whether they use rhCG or uhCG in a well defined patient population. We evaluated the outcomes of IVF therapies done with rhCG or uhCG products between February, 2008 and January, 2009.

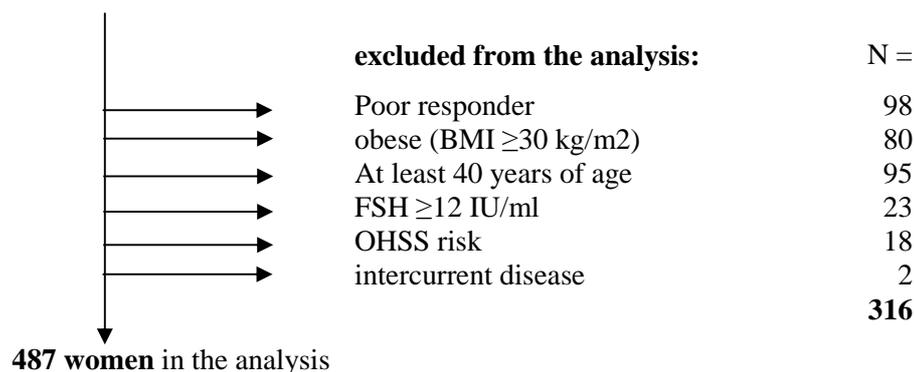
### **Results**

In the evaluated period 803 IVF interventions were performed in our Centre. We excluded unresponsive or obese patients; those above 40 years of age; and those with an FSH level >12 NE/ml (n = 296), as our Institutional Guidelines recommends the preferential use of rhCG in this population. Clinical signs and symptoms suggesting OHSS occurred in 15 and 3 of rhCG and uhCG treated patients, respectively. The implantation should have been cancelled due to concomitant disease in two patients. Finally, the pregnancy outcomes were compared in 391 and 96 patients treated with rhCG and uhCG, respectively (see Table 2).

### **Discussion**

The results of our observational study indicate that the rate of pregnancies verified by laboratory tests increases by about 13% when rhCG products are used. In addition, we also detected an about 7% (not significant) increase in pregnancies entering the 24<sup>th</sup> week of gestation.

803 women subjected to IVF between 02/2008 and 01/2009



**Clinical characteristics**

	<b>rhCG</b>	<b>uhCG</b>	
n =	391	96	
Age (years)	32.5 $\pm$ 3.5	33.3 $\pm$ 3.7	
BMI (kg/m <sup>2</sup> )	21.9 $\pm$ 2.6	22.5 $\pm$ 2.6	
No. of previous attempts	1 $\pm$ 1	0.5 $\pm$ 1	
Endometrium thickness (mm)	12 $\pm$ 2	11.5 $\pm$ 2	
<b>Therapeutic characteristics</b>			
GnRH agonists	159	46	
GnRH antagonists	232	50	
6500 IU dose	100	-	
9750 IU dose	253	-	
13000 IU dose	38	-	
<b>Pregnancy outcomes</b>			
Laboratory verified pregnancy (n =)	169	29*	Total: 198
Pregnancy over 24th g.w (n =)	110	20	130
Laboratory verified pregnancy (%)	43%	30%	40.6%
Pregnancy over 24th g.w (%)	28%	21%	26.7%

p = 0.021, Chi-square-test

**Table 2.** Patient enrolment, clinical characteristics and outcomes. Abbreviations: rhCG: recombinant human chorionic gonadotropin; uHCG: urinary human chorionic gonadotropin; BMI: body mass index; GnRH: gonadotrop-releasing hormone; IU: international unit; g.w: gestational week

As these patients were highly heterogeneous, these observations were adjusted for patients' clinical characteristics. The associations remained

significant and the beneficial impact of rhCG on ongoing became almost significant as well. Although our retrospective analysis does not allow the exact determination of underlying cause, it is reasonable to postulate that one factor responsible for increased success rate may be the possibility of individualized therapy with rhCG products, as rhCG products are available in different dosing formulations. In addition, the batch variability of rhCG products is negligible (in contrast with uhCG products).

### **C. WHICH PROTOCOL FOR THE PRETREATMENT OF ENDOMETRY BEFORE THE IMPLANTATION OF FROZEN-THAWED EMBRYO IS THE MOST EFFECTIVE APPROACH IN TERM OF PREGNANCY RATE?**

Different IVF centres apply different approaches and protocols for the pre-treatment of endometry with gonadotropins / GnRH agonists before the implantation of frozen-thawed embryo (FET). The aim of our retrospective data analysis was to elucidate whether success rates after FET based on natural, programmed or stimulated cycles differ.

#### **Methods\***

FET was applied in women with natural cycles (ovulating women), or after pre-treatment with E2 and P or after a hMG/rFSH stimulated cycle. If the size of oocyte was larger than 20-24 mm and endometrial thickness was higher than 10 mm, 10,000 IU rhCG or hCG was administered.

FET was performed on Day 17 – 20 of the cycle. At this time point P was given to support luteal phase. In women with hormonally manipulated cycles down-regulation was performed during the mid-luteal phase of preceding cycle. Then the development of endometry was supported with the administration of 17  $\beta$  E2 in increasing doses until the thickness of endometry reached 8 mm. At this time P was administered to support the luteal phase; FET was performed on Day 17 – 20. In women treated with hMG or rFSH the hormonal therapy was performed with low doses (75 and 50 IU/day, respectively). The dose of gonadotrop hormone was gradually increased until the developing oocyte's diameter and E2 levels were sufficiently large (i.e. 17 – 18 mm and >300–350 pg/ml, respectively).

Ovulation was induced by the administration of 5,000 - 10,000 IU rhCG or uhCG and 3 days later FET was performed. Luteal phase was supported by P in this protocol.

## Results

Between 2002 and 2007 we applied 2207 FET cycles. In average, a 30% pregnancy rate was detected (668 pregnancies from 2207 FET) (Table 3). The type of protocol used for pre-treatment of endometry had no significant effect on pregnancy rate; however, this rate was tended to be the highest with natural cycle.

	<b>Cycle No.</b>	<b>Successful pregnancy</b>	<b>Pregnancy rate</b>
Protocol applied			
Natural cycle	1068	374	35%
Programmed cycle	558	156	28%
Stimulated cycle	581	138	24%.
Implanted embryo			
D3 embryos	1953	572	29%
D5 embryos	254	96	38%

**Table 3.** Pregnancy rates with FET cycles

The highest pregnancy rate of 38% was reached with the implantation of D5 embryos; the pregnancy rate with D3 embryos was nominally lower (29%).

Comparing the different protocols used for pre-treatment of endometry no difference in result was detected; however, nominally the highest pregnancy rate occurred with spontaneous cycles without administration of any drug.

## Discussion

A number of factors have an impact on success rate after FET cycles. One of the still unclarified issues is whether exogenous administration of E2 may improve results obtained with natural cycles. The results of our analysis reinforce our earlier observations done in our Institute and in other centres: the success rates are comparable after natural-cycle based, programmed or stimulated protocols. This suggests that hormonal support does not increase the rate of pregnancies. Instead, the success rate was nominally higher by about 9% after natural cycles.

Protocols used for pre-treatment of endometry during FET should be decided always after careful consideration of the patient's individual needs. In case of a sequentially designed FET the first step is always the approach based on spontaneous natural cycles; if this is unsuccessful, the next steps are the programmed and stimulated cycles.

### **D. DOES BETA HCG VALUES MEASURED ON DAY 14 AFTER FERTILIZATION OF OOCYTE HAVE ANY PREDICTIVE VALUE DURING IVF THERAPY?**

The several attempts with ART and IVF may present an almost intolerable strain for the infertile couple, therefore it is a must to have a definitive and early data about the success of therapy. The measurement of  $\beta$ -hCG levels is a possible candidate. However, literary data and current practice in Hungary are not unequivocal regarding the timing of  $\beta$ -hCG measurements after a blastocyst culture.  $\beta$ -hCG levels in the same embryonal age are lower following blastocyst transfer than those measured after 'traditional' transfers performed on Day 2-3 after oocyte retrieval or in spontaneous pregnancies. The explanation of this phenomenon is the lower cell volume after blastocyst culturing compared to 'traditional' transfers or spontaneous pregnancies.

The blastocyst cultures were introduced in our Centre at the beginning of 1999. We performed an analysis in 2002 in order to elucidate the predictive value of  $\beta$ -hCG levels on Day 14 after oocyte retrieval.

## **Patients and methods\***

Between 2nd January, 2001 and 31st December, 2002 we measured increased  $\beta$ -hCG levels on Day 14 after oocyte retrieval in 520 patients after IVF-ET treatment. ET was performed on Day 2, 3 or 5 after fertilization.  $\beta$ -hCG levels were measured on Day 14 after oocyte retrieval. The level of detection was 2 IU/L. Pregnancies were biochemical, if the only sign was an increased hCG level without further clinical signs and symptoms or characteristic US signs. Clinical pregnancy was defined as the presence of US signs of in utero embryo, its heart functions or extrauterine pregnancy.

## **Results**

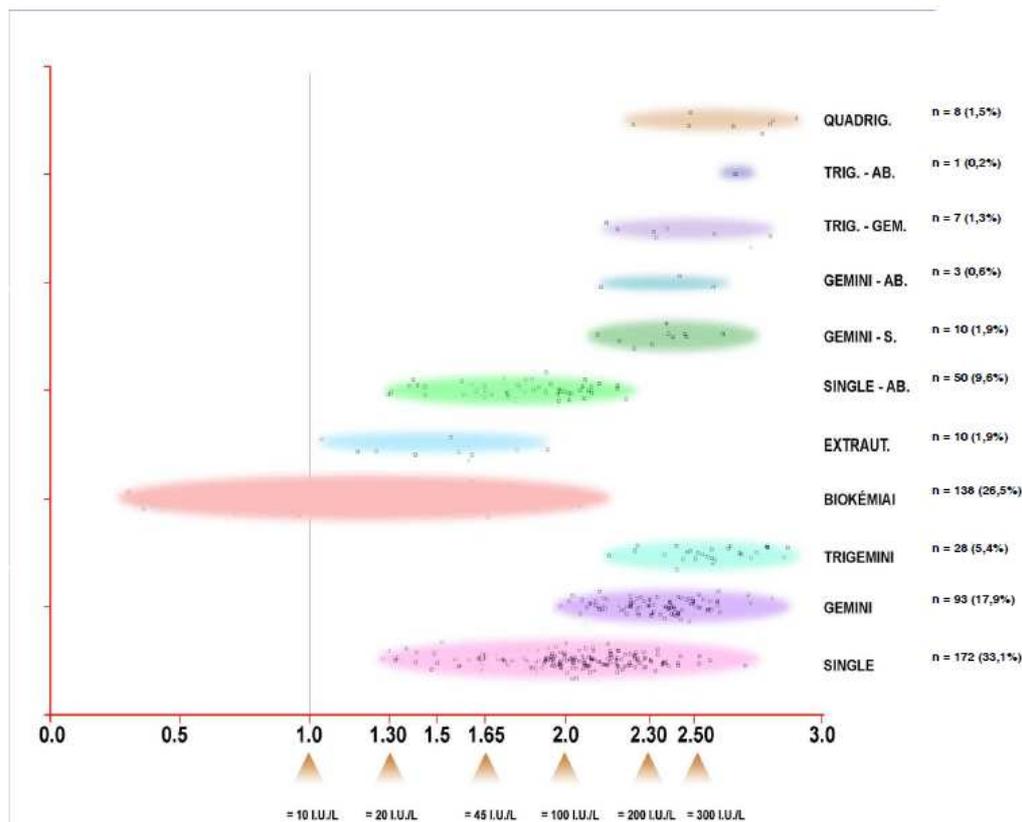
Out of the 520 cases, the number of clinical and biochemical pregnancies was 382 (73.5%) and 138 (26.5%), respectively.

$\beta$ -hCG levels measured on Day 14 after oocyte retrieval indicate that if 45 IU/L is used as cut-off value, the sensitivity and specificity of  $\beta$ -hCG levels for the discrimination between clinical and biochemical pregnancies are 91.1% and 89.9%, respectively.

## **Discussion**

The single measurement of  $\beta$ -hCG levels on Day 14 after oocyte retrieval is suitable exclusively for the prediction of clinical pregnancies and early pregnancy loss in singular pregnancies (Figure 1). In multiple pregnancies, however, this parameter does not help to assess the risk of gemini reduction and/or early pregnancy loss.

In the analyzed period the rate of extrauterine pregnancies after IVF-ET was 2,6% (that is lower than the internationally reported 4-5% rate). Of note, in 8 of 10 extrauterine pregnancies the  $\beta$ -hCG levels were below 45 NE/L (median value of  $\beta$ -hCG was 32.4 NE/l). In monitoring and follow-up of these cases the value of a single determination of  $\beta$ -hCG on Day 14 after oocyte retrieval may be limited, as the early recognition of extrauterine pregnancies is in fact based on serial  $\beta$ -hCG measurements and, above 1025 IU/L  $\beta$ -hCG levels, on highly sensitive US techniques.



**Figure 1.**  $\beta$ -hCG levels according to induced pregnancies. TRIG = trigemini, AB = abortus, TRIG – GEM = trigemini – gemini reduction, EXTRAUT = extrauterine, SINGLE = singular pregnancies

## E. WHAT ARE THE LIMITATIONS OF ULTRASOUND WHEN ECTOPIC IVF-ET PREGNANCIES ARE ASSESSED?

The recent spread of highly sensitive US instruments and transvaginal transducers improved our capability to early recognition of extrauterine pregnancies. As a result, the role of previously used standard classical methods such as abrasion or puncture of Douglas cavity in the detection of extrauterine pregnancies decreased. However, we should be aware of the limitations of US technique and the diagnostic value of the serially determined  $\beta$ -hCG levels.

### Methods\*

In general, the first US test is performed on the 5<sup>th</sup> week of gestation. The rationale behind this practice is to recognize the early extrauterine pregnancies after IVF-ET; it is well known, that this complication is more

frequent in ART compared to spontaneous pregnancies (2-11% IVF-ET versus 0,6-0,8%). If US suggests no in utero pregnancy,  $\beta$ -hCG levels are measured immediately. Based on  $\beta$ -hCG levels we make any of the following decisions:

1. Watchful waiting with serial measurement of  $\beta$ -hCG levels on every second day.
2. MTX treatment under strict monitoring of  $\beta$ -hCG levels and US control.
3. Hospitalization and, in case of necessity, immediate laparoscopy (laparotomy). If salpingectomy is not performed, further  $\beta$ -hCG measurements are done to establish the efficacy of intervention.

Of course, Decision 1 or 2 is made when an intact egg sac is detected in any tube, or, in its absence, there is no echo suggesting bleeding in the Douglas cavity.

## **Results**

Between 2<sup>nd</sup> January, 2001 and 30<sup>th</sup> April, 2008 we performed 6647 IVF-ETs. Extrauterine pregnancy was detected in 45 cases (representing 2.06% of all the 2189 clinical pregnancies).

The geometric mean of  $\beta$ -hCG measured on Day 14 of pregnancy was 36.3 IU/L in these 45 extrauterine gravities. (In our previous analysis, 45 IU/L was that cut-off value that had 91.1% sensitivity and 89.9% specificity for the discrimination between biochemical and ongoing pregnancies). In 42 patients we were able to monitor  $\beta$ -hCG levels. The normal doubling time of 1.4 – 2.1 days was measured just in 8 subjects.

## **Discussion**

Transvaginal US technique provides an opportunity to visualize in utero or, sometimes, the extrauterine sac, provided that  $\beta$ -hCG levels are above 1025 IU/L. However, even colour coded Doppler technique is not appropriate for the identification of pregnancies when  $\beta$ -hCG levels are <800-1000 IU/L. A warning sign of extrauterine pregnancies is when the first  $\beta$ -hCG level is low, does not correlate with gestational age or when the doubling time of serial  $\beta$ -hCG levels is delayed (i.e. consecutive  $\beta$ -hCG levels do not increase exponentially).

Serial measurement of  $\beta$ -hCG levels as a complementary technique to vaginal US provides an opportunity to recognize and monitor extrauterine pregnancy and, also, helps to assess the efficacy of methotrexate therapy. Our data indicate that just one third of all extrauterine pregnancies could be diagnosed by US in early phase and two-thirds of them  $\beta$ -hCG measurements are required to diagnose this complication. Therefore, irrespectively of the use of highly sensitive US techniques one should also measure repeatedly  $\beta$ -hCG levels to diagnose and monitor IVF-ET ectopic pregnancies. One cannot overemphasize how important is to establish this diagnosis in the possibly earliest phase in an era of laparoscopic surgical interventions.

## **F. IS THE RISK OF ANNEX TORSION INCREASED AFTER AN IVF-ET?**

Our efforts during IVF treatment cycles aim to obtain multiple mature oocytes. As a result of COH the volume and mass of ovaries are dramatically increased and several fold higher than that of the normal. The large ovaries resembling to Ementhaler cheese are filled with lutein cysts. In case of pregnancy (that is characterized by susceptibility for systemic oedema and looser connective tissues) the large ovaries increase the risk of annex torsion. However, this complication is quite rare; in another Hungarian IVF centre one case was reported after 5132 IVF-ET treatments. In our centre, 3 cases with annex torsion occurred from 2926 IVF-ET therapy.

These cases required dramatically different interventional approach because of different anatomical situation and different gynaecological expertise. Laparoscopy was performed in 2 of the 3 cases (of those, 1 was terminated by laparotomy). However, the interventions were successful and allowed the development of healthy pregnancies. (Each of this pregnancies, however, also supported by P up to 12<sup>th</sup> week of gestation; then the luteoplacental shift successfully occurred.)

These cases indicate that in pregnancies after ART the risk of annex torsion is increased. During early pregnancy after IVF-ET one should rather suspect annex torsion in the presence of characteristic signs and symptoms of annex torsion such as lower abdominal cramps. The very early recognition of torsion provides an opportunity to perform an up-to-date, laparoscopic and organ-sparing intervention for detorquation. If conservative approach is decided, in addition to the decrease of the size of the ovary one should perform the fixation of ovaries in order to prevent any relapse of this condition.

## THESES

1. The successful pregnancy rates after controlled ovary hyperstimulation with GnRH agonist long protocol or GnRH antagonist protocol during IVF (ICSI)-ET are comparable.

2. The use of recombinant hCG (rhCG) during IVF treatment leads to a significantly greater rate of laboratory verified pregnancies and a numerically greater rate of clinical pregnancies in comparison with the use of urinary hCG (uhCG).

3. During frozen-thawed embryo transfers there is no significant difference in clinical pregnancy rates after different protocols used for the preparation of endometry. There is a tendency, however, that the highest rate of pregnancy is achieved with protocols based on natural cycles.

4. On Day 14 after the oocyte retrieval the laboratory verified pregnancies and clinical pregnancies can be distinguished with a specificity and sensitivity of 89.9% and 91.1%, respectively, if the cut-off level of serum  $\beta$ -hCG is 45 IU/L.

5. Transvaginal ultrasound is not a suitable tool to recognise exactly the presence of ectopy pregnancy early; however, serial  $\beta$ -hCG measurements provide an opportunity to diagnose extrauterine gravidity that, hence, can be operated in intact state. In addition to patient's monitoring with serial  $\beta$ -hCG and ultrasound the wait-and-see approach and medical therapy (including methotrexate) are also justified and can be used safely.

6. During the early phase of pregnancies initiated with artificial reproduction therapies the annexes should be assessed with extra caution with transvaginal ultrasound in order to early recognize the warning signs of annex torsion as the incidence of this complication is higher than the average after controlled ovary hyperstimulation as it is also suggested by our cases.

## SCIENTIFIC PUBLICATIONS RELATED TO THESE

### PAPERS

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5. Zeke J, Skriba Eszter, Szűcs Zoltán, Konc J: Az ultrahangvizsgálatok korlátai IVF-ET útján fogant méhen kívüli terhességek kivizsgálásában és kezelésében Magyar Nőorvosok Lapja, 74, 25-28 (2011).
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### POSTERS AND LECTURES

#### POSTERS

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Several factors determine the success of assisted reproduction techniques. The most important ones include the expertise and professionalism of ART team.

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