FETOSCOPY AND EMBRYOSCOPY
an old story but a new challenge
ESGE 2005, Athens

Vasilios Tanos MD, PhD
Vis. Prof. in Obstetrics and
Gynaecology
Terminology

- Embryoscopy - is the examination of the embryo before 12 weeks of gestation by introducing the endoscope into the exocoelomic space (previous to fusion of the chorion and amnion) either by trans-cervical or trans-abdominal route.

- Fetoscopy - usually 14-28 weeks, the endoscope is introduced directly in the amniotic cavity. Phenotypic evaluation added to the karyotype analysis.

Should be restricted to families at high risk for recurrence of genetic conditions associated with external fetal anomalies not detectable by ultrasound.
Fetoscopy and Embryoscopy

- Since 1954 used for diagnosis of phenotype
  (Westin B. – Lancet)

- Since 1968 used to guide
  Chorion villus sampling
  Percutamenous umbilical blood sampling
  Fetal muscle, skin and liver biopsies
Technological advances...

The recent optic and instrument technological advances offer better visualization with smaller diameter telescopes, enable better and broader spectrum of diagnostic capabilities.

Also enable minimal operative procedures to the fetus with less complications for the fetus and the mother.
Minimal invasive operations to the fetus compared to open fetal surgery

- Smaller uterine puncture sites are required
- Reduced risk for
  1. preterm labor
  2. amniotic fluid leak
  3. hemorrhage

Larger number of different pathological diagnoses will benefit from these procedures.
Fetal pathologies treated with fetoscopy surgery

- Duchenne muscular dystrophy
- Lower urinary tract obstruction
- Pulmonary hypoplasia
- Sacrococcygeal Teratoma
- Myelomeningocele
- Amniotic Band Syndrome

Complications with monochorionic twins
- Anomalous co-twin with threatened fetal demise
- Twin reversed arterial perfusion sequence
- Twin-twin transfusion syndrome
- TRAP sequence
Fetal muscle biopsy

Duchenne muscular dystrophy - dystrophin deficiency
1:3500 Males, X-linked recessive trait, 30% de novo mutations

Using US fetal gluteal muscle biopsy is performed
Complications: Serious injuries to the nerves and veins

Fetoscopy: Using 1mm endoscope inserted lateral to the biopsy forces through a 19G trocar sleeve guided the biopsy forceps into the posterior lateral segment of the fetal buttock.

However most of mm bxs are performed by ultrasound biopsy
Therapeutic Fetoscopy

Lower urinary tract obstruction

leads to oligohydramnios, pulmonary hypoplasia and cystic renal dysplasia.
Mainly males, etiology posterior urethral valve, urethral atresia and urethral hypoplasia.

Early reversal of obstruction in midgestation can prevent renal damage by vesico-amniotic diverting shunts.

Treatment: Functional shunt failure 40 - 50% due to shunt displacement.
Laser ablation of the posterior urethral valves: Technically succeed but no long term survivors.
Crombleholme T.M. and Johnson MP did diagnostic cysto-urethroscopy using 1mm semi-rigid fiberoptic endoscopic system

They could differentiate between maximal urethral obstruction and urethral atresia and posterior urethral valves
Congenital Diaphragmatic Hernia

Pulmonary hypoplasia
Treatment: Tracheal occlusion can reduce the risk of
  Respiratory Distress Syndrome
  Pre Term Labor

US guided insertion of endotracheal balloon
Complication: Vocal cord paralysis

Fetoscopic guided endoluminal balloon
Sacroccocygeal Teratoma

Complications:  Placentomegaly
            Hydrops
            Prematurity
            Tumor hemorrhage at delivery

Resection of tumor in utero can prevent above complications

Fetoscopic laser approach .. But can cause
Ischemic necrosis of the anorectal sphincter mass
Superficial vessels are accessible but not the deep ones

Probably Radiofrequency Ablation can offer better results
Myelomeningocele

Treatment:
Maternal split thickness skin can be applied over the defect secured by suricel or fibrin glue at 22 and 24 weeks.

None survived
Amniotic Band Syndrome

The earliest diagnosis is 12 weeks by Vaginal ultrasound.

Constrictive bands can cause:
- Umbilical cord constriction
- Affect fetal anatomy
- Cranio facial and limb deformities

Quintero et al performed first fetoscopic lysis of amniotic bands in human fetuses.

However PROM and Pre Term Labor
Monochorionic Twins Complications treated by Fetoscopy

1) Anomalous co-twin with threatened fetal demise.
2) Twin reversed arterial perfusion sequence
3) Twin-twin transfusion syndrome.

Treatment:
- Fetoscopic cord ligation of the affected twin (2-port technique)
- Fetoscopic coagulation when anomalous co-twin threatened the normal twin
The acardiac / acephalic twin receives all of its blood supply from the normal fetus (pump twin).

On the chorionic plate arterial-arterial and venous-venous anastomoses cause “TRAP sequence”, which cause reverse hemodynamic perfusion, and abnormal development.
Embryoscopy

- First trials presented minor benefits and limited diagnostic potentials due to poor technical facilities.

- Recent US improvements, increased use of US, and earlier gestational age US screening will lead to earlier diagnosis of embryo/fetal defects.

- Recent molecular biology achievements and technical advances (US, endoscopes, etc) as well as social needs and demands will accelerate the clinical application of embryoscopy complementary to US for early diagnosis and probably embryo treatment...
The role of Embryoscopy

- **Diagnostic**
  - Reevaluate normal embryo status
  - Phenotype of embryos with suspected US abnormalities
  - Etiology of Recurrent abortions

- **Therapeutic**
  - Cervical ectopic pregnancy
  - Stem cell therapy
  - Gene therapy

Disadvantage: Fear of affecting the development of the optic nerve when the procedure is performed after weeks of gestational age
In Vivo Evaluation of early embryo development

- Cervical canal
- Intrauterine cavity
- Pregnancy sac
- Chorion and amnion
- Embryo
- Umbilical cord
- Alantois
Watch the above video at http://medtube.net/obstetrics-and-gynecology/medical-videos/11150-embryoscopy
Cervical Ectopic Pregnancy

- US evaluation at 5+4 weeks.
- Mild bleeding
- Pregnancy G4 after 3 TOPs
- Embryoscopy in order to inject methotrexate
Watch the above video at http://medtube.net/obstetrics-and-gynecology/medical-videos/11212-cervical-ectopic-pregnancy
Watch the above video at http://medtube.net/obstetrics-and-gynecology/medical-videos/11156-cervical-ectopic-pregnancy
Embryoscopy: Searching for the Etiology of Recurrent Spontaneous Abortions

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Vasilios Tanos MD, PhD
Aretaeion Hospital

Demetra Georgiou BSc, Dipl.Gen, PhD
MakI11. Hospital, Dpt Cytogenetics

Eleftherios Meridis, MD
Minas Paschopoulos MD
Ioannina University Hospital,
Dpt Obstetrics and Gynaecology, Ioannina, Greece
Recurrent spontaneous abortions (RSA) refer to three or more consecutive spontaneous abortions (Hannes 1992).
Abortion Risk (Poland et al. 1977)

- Risk for SA after 1st Abortion 20-25%
- Risk for SA after 2nd Abortion 40-50%
- Risk for SA after ≥ 3rd Abortion 60% and levels of
Without considering any specific cause most couples have at least a 60% chance of delivering a live-borne infant with three or more spontaneous abortions.
RSA due to Male factor

Influence sperm quality and result in early embryo loss
(Hamamah S et al. 1997)

- Ageing (increased risk for trisomy 21 if paternal age >55)
- Occupation - exposure to toxic material
- Environmental exposure
- Smoking
Mechanism

Alterations in sperm chromatin – defective DNA decondensation and activation in the nucleus during fertilization and delay in the formation of the male pronucleus and/or the first division events
The frequency of factors affecting RSA
(Dhont M. 2003, Kuttech WH 1999)

a) Genetic abnormalities 3-5%
b) Uterine anatom. abnor. (hereditary & acquired 15-20%)
c) Immunologic (Antiphosphol. & Anticardiolipin 15-25%)
d) Endocrine / metabolic disorders 5-8% (DM, PCOD etc)
e) Environmental factors 5-10% (occupation, smoking etc)
f) Unexplained 40% can not identify the etiology
(Stephenson MD 1996)
Implantation factors
(Jokimaa et al 2002 and 2003)

- Altered expression of genes involved in the production and degradation of endometrial extracellular matrix (ECM)
- Mid-secretory phase endometrium found
- Higher mRNA levels of type I collagen, MMP-2 and cathepsin H,
- Decreased mRNA levels of TIMP-3
Patients and Methods

- 25 patients with history of RSA
- All patients underwent history, general body and gynecological examinations and laboratory investigations and hysteroscopy during their last abortion.
Patients

Our study - RSA patients with

- unexplained etiology 13
- uterine cavity abnormalities corrected 5
- anticardiolipin syndrome 2
- endocrinological factor 3
- Treated with heparine 6
- Treated with husband WBC 1
Embryoscopy

- Technique of visualization of the human embryo - up to the age of 12 weeks

- Instruments: Telescope 3.5mm, 30°, single flow, TransCervical
  - Metal Halide light source 270 Watts

- Distention medium: Normal saline

- No use of anesthesia or sedation
Embryoscopy: Targets of the Study

- Standardization of the technique.
- Evaluation of the potentials of the technique.
- Evaluation of the characteristics of the pregnancy sac and its contents.
- Correlation of the embryo external characteristics and its genetic analysis.
(A) History, trans-vaginal ultrasound findings, embryo external characteristics and karyotype of all 23 RSA cases managed with transcervical-embryoscopy

<table>
<thead>
<tr>
<th>S/ N</th>
<th>PI</th>
<th>Age</th>
<th>History and related facts</th>
<th>G</th>
<th>P</th>
<th>A</th>
<th>b</th>
<th>C</th>
<th>h</th>
<th>GA weeks</th>
<th>TVU findings</th>
<th>Embryoscopy Findings / Phenotype</th>
<th>Karyotype</th>
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<tbody>
<tr>
<td>1</td>
<td>ZM</td>
<td>36</td>
<td>Unexplained RSA</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8+4</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>46XY</td>
<td></td>
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<tr>
<td>2</td>
<td>MM</td>
<td>26</td>
<td>Polycystic ovarian syndrome</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>Normal</td>
<td>Low set ears. Short neck</td>
<td>47XY+21</td>
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<tr>
<td>3</td>
<td>LA</td>
<td>33</td>
<td>IVF due to OTA - Twin Pregnancy</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>2 sacs 1 embryo CRL4mm</td>
<td>2 sacs. 1-embryo-pole only</td>
<td>92XXXY</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>TN</td>
<td>32</td>
<td>Unexplained RSA</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9+3</td>
<td>Normal</td>
<td>Both embryos normal</td>
<td>Infected sample</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>KP</td>
<td>31</td>
<td>Twin Pregnancy after ovarian stimulation. Anovulatory cycles.</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7+3</td>
<td>Normal 2 sacs</td>
<td>Normal female thickened NT</td>
<td>45X0</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>SB</td>
<td>25</td>
<td>Unexplained RSA</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>Nuchal Translucency thickened</td>
<td>Abnormal procencephalon left flank protuberation malformation</td>
<td>46XX</td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>ZT</td>
<td>29</td>
<td>Unexplained RSA. Treated with low molecular heparine.</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>CRL5mm</td>
<td>Anencephaly Abdominal malformation and leg abnormal development</td>
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<td></td>
<td></td>
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<tr>
<td>8</td>
<td>PPM</td>
<td>37</td>
<td>Unexplained RSA. Treated with low molecular heparine.</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>8+5</td>
<td>Blighted ovum</td>
<td>String embryo prickly alantois</td>
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<td></td>
<td></td>
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<tr>
<td>9</td>
<td>AT</td>
<td>36</td>
<td>IVFx7, due to severe OTA</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>CRL 4mm</td>
<td>Nodular embryo with threads</td>
<td>47XX+6</td>
<td></td>
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<tr>
<td>10</td>
<td>ZAG</td>
<td>38</td>
<td>Septate Uterus, operated twice</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>7+3</td>
<td>CRL 18mm</td>
<td>Abnormal procencephalon left flank protuberation malformation</td>
<td>47XY+21</td>
<td></td>
<td></td>
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<tr>
<td>11</td>
<td>KAM</td>
<td>24</td>
<td>Unexplained RSA</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>6+4</td>
<td>Blighted ovum</td>
<td>Amniotic cavity with pseudo appearance of molar like pregnancy</td>
<td>92XXYY</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(B) History, trans-vaginal ultrasound findings, embryo external characteristics and karyotype of all 23 RSA cases managed with transcervical-embryoscopy

<table>
<thead>
<tr>
<th>S/ N</th>
<th>P I</th>
<th>Age</th>
<th>History and related facts</th>
<th>G</th>
<th>P</th>
<th>Ab</th>
<th>Ch</th>
<th>GA weeks</th>
<th>TVU findings</th>
<th>Embryoscopy Findings / Phenotype</th>
<th>Karyotype</th>
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</thead>
<tbody>
<tr>
<td>12</td>
<td>HAA</td>
<td>40</td>
<td>RSA – intramural big fibroids 17 weeks enlarged uterus.</td>
<td>5</td>
<td>0</td>
<td>3(2)</td>
<td>0</td>
<td>9</td>
<td>CRL 16mm</td>
<td>Missing right eye, procencephalon malformation stricture of the cord at the placental side.</td>
<td>46XX</td>
</tr>
<tr>
<td>13</td>
<td>LD</td>
<td>40</td>
<td>Unexplained RSA. Last pregnancy diagnosed a 15mm fibroid adjacent to the endometrial cavity.</td>
<td>6</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>Blighted ovum</td>
<td>String embryo attached to alantois</td>
<td>47XY+15</td>
</tr>
<tr>
<td>14</td>
<td>LD</td>
<td>41</td>
<td>As above but fibroid 23mm adjacent to the endometrial cavity</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>Blighted ovum</td>
<td>Fetal mass without clear characteristics</td>
<td>47XX+16</td>
</tr>
<tr>
<td>15</td>
<td>TM</td>
<td>27</td>
<td>RSA, Azospermic husband and Sperm Donation was used</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>6+3</td>
<td>Blighted Ovum</td>
<td>String embryo underdeveloped</td>
<td>47XY+21</td>
</tr>
<tr>
<td>16</td>
<td>XP</td>
<td>30</td>
<td>Polycystic ovarian syndrome, Unexplained RSA and treated with immunoglobulins</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>6+5</td>
<td>CRL 9mm</td>
<td>Nodular embryo, abnormal shrink alantois</td>
<td>47XX+6</td>
</tr>
<tr>
<td>17</td>
<td>MF</td>
<td>32</td>
<td>IVF x 1 due to unexplained infertility</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>CRL 8mm</td>
<td>Normal</td>
<td>45X0</td>
</tr>
<tr>
<td>18</td>
<td>MF</td>
<td>33</td>
<td>IVF x 2, Unexpl. Infert, + HBP, DM</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>9</td>
<td>CRL 25mm</td>
<td>Normal, clots in the uterine cavity</td>
<td>46XY</td>
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<tr>
<td>19</td>
<td>LT</td>
<td>35</td>
<td>Septate uterus operated</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>10+2</td>
<td>CRL 36mm</td>
<td>Macerated embryo, underdeveloped</td>
<td>47XY+21</td>
</tr>
<tr>
<td>20</td>
<td>ZE</td>
<td>27</td>
<td>Immunization with husbands WBC</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>7+1</td>
<td>CRL 12mm</td>
<td>Maldevelopment</td>
<td>46XY</td>
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<tr>
<td>21</td>
<td>ST</td>
<td>34</td>
<td>Anti-Cardiopilin Sy – treated with heparine</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>6+3</td>
<td>CRL 7mm</td>
<td>Abnormal</td>
<td>47XX+15</td>
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<td>CSM</td>
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<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>Blighted ovum</td>
<td>Stricky embryo</td>
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</tr>
<tr>
<td>23</td>
<td>LK</td>
<td>37</td>
<td>HBP, DM</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>10</td>
<td>CRL 40mm</td>
<td>Blood clots /bad visualization</td>
<td>infected</td>
</tr>
</tbody>
</table>
Results

- The total of 23 embryos were evaluated.
- In 21/23 cases embryoscopy was successful and complete evaluation of the embryo and pregnancy sac was performed.
- The beta-hCG serum level was zero in three weeks after the D&C.
Correlation of the embryo morphology and embryo karyotype

<table>
<thead>
<tr>
<th>Variety of possibilities</th>
<th>Cases</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>A Normal phenotype and normal karyotype</td>
<td>3/21</td>
<td>14</td>
</tr>
<tr>
<td>B Normal phenotype and abnormal karyotype</td>
<td>1/21</td>
<td>5</td>
</tr>
<tr>
<td>C Abnormal phenotype and normal karyotype</td>
<td>3/21</td>
<td>14</td>
</tr>
<tr>
<td>D Abnormal phenotype and abnormal karyotype</td>
<td>14/21</td>
<td>67</td>
</tr>
</tbody>
</table>
Embyroscopy of Missed Abortion

In 233 cases, Philipp T et al. in 2003, found

- 75% with abnormal karyotype,
- 18% - abnormal phenotype and normal karyotype compared to [14% our results SRA]
- 7% - normal phenotype and karyotype compared to [14% our results SRA]
Investigation of RSA etiology

- Rubio Carmen et al. 2004 (MSRM)
- RSA couples undergoing PGD compared to those cases that did not have RSA
- Numerical chromosomal abnormalities in human preimplantation embryos of women with RSA was 66% as compared to 33% found in non RSA patients.
29 y old, M+1

G1-G3 Recurrent Abortions

Complete Workup for RA – normal results

G4 - Crystal Heparine and LMH – term pregnancy healthy baby

G5 - CH + LMH at 6 weeks missed abortion - Embryoscopy
Embryoscopy revealed
- Anencephany
- Abdominal malformation
Watch the above video at http://medtube.net/obstetrics-and-gynecology/medical-videos/11152-embryoscopy
40y old, 2yM+0,
Subserous & Intramural fibroids
Uterus enlarged 17w,
G5, Ab(2) 3
Recurrent Abortions
Embryo missing right Eye
Watch the above video at http://medtube.net/obstetrics-and-gynecology/medical-videos/11149-embryo-missing-right-eye
Conclusions

- Embryoscopy seems to be a valuable tool in identifying the etiology in spontaneous recurrent abortions. This can be especially useful for future treatment purposes.

- The embryo external characteristics differ in cases of the same genetic abnormalities.

- Both Alantois and Chorion seem to be affected from the genetic abnormality expressed by the embryonal tissue.