How can surgery increase the success rate of ART?

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Grado, May 2011

How can surgery improve the results of ART?

- Intra-uterine pathology
- Structural uterine anomalies
- Distal tubal disease
- Endometrial scratch

Hysteroscopy

- RCT by Demirol & Gurgan (2004)
- 421 women with 2 or more IVF failures
- 56 out of 210 (26%) women with normal HSG had intrauterine lesions detected by office hysteroscopy, and treated
- The subsequent pregnancy rate in the treated group (30.4%) and the group with normal hysteroscopy (32.5%) was significantly higher than the group who did not undergo hysteroscopy (21.6%)
Will Hysteroscopy Improve Outcome of Recurrent Implantation Failure?

Bosteels, J. et al. Hum Reprod Update 2010
Systematic Review and meta-analysis

- Effects of office hysteroscopy (in the preceding menstrual cycle) on outcome of further IVF after two failed attempts

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Fibroids and infertility: an updated systematic review of the evidence
Elizabeth A. Potts, M.D.,* William H. Parker, M.D.,* and David L. Office, M.D.*

**Table 3**
Effect of fibroids on fertility: submucous fibroids.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancy rate</td>
<td>4</td>
<td>0.363</td>
<td>0.179-0.737</td>
<td>P &lt; .003</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>2</td>
<td>0.363</td>
<td>0.128-0.690</td>
<td>P &lt; .003</td>
</tr>
<tr>
<td>Ongoing pregnancy/live birth rate</td>
<td>2</td>
<td>0.218</td>
<td>0.115-0.410</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Spontaneous abortion rate</td>
<td>2</td>
<td>1.678</td>
<td>1.373-2.051</td>
<td>P &lt; .002</td>
</tr>
<tr>
<td>Preterm delivery rate</td>
<td>0</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Polypectomy in Subfertile Patients with Polyps Undergoing IUI

Outcome: Clinical pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Hysteroscopic polypectomy</th>
<th>Diagnostic hysteroscopy</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>No effects</td>
<td>4</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>4-9</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>10 and more</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

RR = 2.3; 95% CI: 1.6-3.2


Summary

Hysteroscopic polypectomy doubles CPR in women undergoing IUI
Intrauterine adhesiolysis (scissors)

How can Surgery improve the results of ART

- Intra-uterine pathology
- Structural uterine anomalies
- Distal tubal disease
- Endometrial scratch
**TABLE 1**

Effect of fibroids on fertility: intramural fibroids.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies/ subsudies</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. All studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation rate</td>
<td>12</td>
<td>0.810</td>
<td>0.699-0.941</td>
<td>P = .006</td>
</tr>
<tr>
<td>Ongoing pregnancy live birth rate</td>
<td>7</td>
<td>0.684</td>
<td>0.507-0.896</td>
<td>P = .01</td>
</tr>
<tr>
<td>Spontaneous abortion rate</td>
<td>8</td>
<td>0.703</td>
<td>0.503-0.848</td>
<td>P = .001</td>
</tr>
<tr>
<td>Preterm delivery rate</td>
<td>1</td>
<td>1.747</td>
<td>1.226-2.489</td>
<td>P = .002</td>
</tr>
<tr>
<td>Breast cancer incidence</td>
<td>1</td>
<td>6.000</td>
<td>0.309-115.806</td>
<td>Not significant</td>
</tr>
<tr>
<td>B. Prospective studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implantation rate</td>
<td>3</td>
<td>0.798</td>
<td>0.407-1.446</td>
<td>Not significant</td>
</tr>
<tr>
<td>Ongoing pregnancy live birth rate</td>
<td>2</td>
<td>0.469</td>
<td>0.291-0.744</td>
<td>P = .19</td>
</tr>
<tr>
<td>Spontaneous abortion rate</td>
<td>2</td>
<td>2.384</td>
<td>1.116-5.122</td>
<td>P = .002</td>
</tr>
<tr>
<td>Preterm delivery rate</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>C. Studies using hysteroscopy in all subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer incidence</td>
<td>1</td>
<td>0.845</td>
<td>0.696-1.071</td>
<td>Not significant</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>1</td>
<td>0.714</td>
<td>0.547-0.831</td>
<td>P = .0013</td>
</tr>
<tr>
<td>Ongoing pregnancy live birth rate</td>
<td>2</td>
<td>0.733</td>
<td>0.363-1.420</td>
<td>Not significant</td>
</tr>
<tr>
<td>Spontaneous abortion rate</td>
<td>2</td>
<td>1.215</td>
<td>0.391-3.774</td>
<td>Not significant</td>
</tr>
<tr>
<td>Preterm delivery rate</td>
<td>1</td>
<td>6.000</td>
<td>0.309-115.806</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

Note: All data were obtained from the literature, as cited in the text.
Classification of congenital uterine anomalies

What is the abnormality?

SEPTUM TRANSECTION
The outcome of singleton pregnancies after IVF/ICSI in women before and after hysteroscopic resection of a uterine septum compared to normal controls

<table>
<thead>
<tr>
<th></th>
<th>Miscarriage rate</th>
<th>Miscarriage rate in matched controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large septum, not removed</td>
<td>83.3%</td>
<td>16.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Small septum, not removed</td>
<td>78.9%</td>
<td>23.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Large septum removed</td>
<td>30.6%</td>
<td>20.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Small septum removed</td>
<td>28.1%</td>
<td>19.3%</td>
<td>NS</td>
</tr>
</tbody>
</table>

How can Surgery improve the results of ART

- Intra-uterine pathology
- Structural uterine anomalies
- Distal tubal disease
- Endometrial scratch

Hydrosalpinges and IVF

The live birth rate of patients with hydrosalpinges undergoing IVF is only one-half that of women who do not have hydrosalpinges
Why does the presence of hydrosalpinges adversely affect IVF pregnancy rate?
- Hydrosalpingeal fluid is embryo toxic
- Hydrosalpingeal fluid contains inhibitors of implantation, thereby impairing endometrial receptivity

Hydrosalpinges and Leukaemia inhibitory factor (LIF) expression in the endometrium
- LIF expression in the mid-luteal phase endometrium of infertile women (n=10) with hydrosalpinges was significantly lower than control fertile subjects
- Salpingectomy resulted in increase of LIF expression in 8/10 subjects with hydrosalpinges
  
  Seli et al 2005
  Human Reprod 20:3012

Hydrosalpinges and integrin expression (αvβ3) in the endometrium
- Integrin (αvβ3) expression in the mid-luteal phase endometrium of women with hydrosalpinges was significantly lower than control subjects
- Salpingectomy resulted in increase of integrin (αvβ3) expression
  
  Meyer et al 1997
  Human Reprod 12:1393
  Bildirici et al 2001
  Human Reprod 16:2422
**Hydrosalpinx and IVF outcome: a prospective randomized multicentre trial in Scandinavia on salpingectomy prior to IVF**

Strandell et al 1999 Human Reprod 14:2762

First IVF cycle, in women with USS visible hydrosalpinges

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>PR</th>
<th>Live birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salpingectomy</td>
<td>35</td>
<td>45.7%</td>
<td>40%</td>
</tr>
<tr>
<td>No salpingectomy</td>
<td>40</td>
<td>22.5%</td>
<td>17.5%</td>
</tr>
</tbody>
</table>

PR, p=0.029  LB, p=0.038

**Hydrosalpinges and IVF**

- Salpingectomy prior to IVF in women with hydrosalpinges improves pregnancy, implantation and live birth rates

- Is it cost-effective to routinely remove all hydrosalpinges prior to IVF?
1. Is it still worth doing surgery if the hydrosalpinx is not visible by ultrasound?
Hydrosalpinx and IVF outcome: a prospective randomized multicentre trial in Scandinavia on salpingectomy prior to IVF
Strandell et al 1999 Human Reprod 14:2762

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>PR</th>
<th>miscarriage</th>
<th>Live birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salpingectomy</td>
<td>112</td>
<td>36.6%</td>
<td>16.2%</td>
<td>28.6%</td>
</tr>
<tr>
<td>No salpingectomy</td>
<td>92</td>
<td>23.9%</td>
<td>26.3%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

PR, p=0.067        LB, p=0.045

2. Is it still necessary to consider surgery in unilateral tubal disease?

Unilateral Hydrosalpinx with a Contra-lateral Patent Tube
McComb & Taylor 2001 Fertil Steril 76:1279

- 23 women with unilateral hydrosalpinx underwent salpingostomy
- IU pregnancy rate 43.5%
- Conclusion – unilateral salpingostomy in women with a contra-lateral patent tube improves fertility
Case History
- 33 year old woman
- one miscarriage at 7 weeks
- Infertility for 15 months
- Conceived spontaneously, but miscarried again at 8 week gestation
- Investigation – L tube normal. R hydrosalpinx, grossly dilated, intraluminal adhesions, salpingectomy.
- Three months later, spontaneously conception, term delivery

3. Is ultrasound guided aspiration of the fluid just as effective?

Surgical Drainage of Hydrosalpinx
Retrospective Analysis
Sowter et al 1997 Human Reprod 12:2147

<table>
<thead>
<tr>
<th></th>
<th>Hydrosalpinx Not seen</th>
<th>Hydrosalpinx Not drained</th>
<th>Hydrosalpinx drained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation</td>
<td>23/239 (9.6%)</td>
<td>4/53 (7.5%)</td>
<td>7/85 (8.2%)</td>
</tr>
<tr>
<td>Live birth per embryo transferred</td>
<td>19/239 (7.9%)</td>
<td>4/53 (7.5%)</td>
<td>5/85 (5.9%)</td>
</tr>
</tbody>
</table>
Ultrasound-guided hydrosalpinx aspiration, RCT
Hammadian et al, Human Reprod 2008

<table>
<thead>
<tr>
<th></th>
<th>Aspiration</th>
<th>No aspiration</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical pregnancy</td>
<td>14/32 (43.8%)</td>
<td>7/34 (20.6%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>10/32 (31.3%)</td>
<td>6/34 (17.6%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Disadvantages of transvaginal aspiration of hydrosalpinges
- Fluid rapidly re-accumulate
- Underlying pathology not altered
- Risk of infection
- Efficacy not proven

Which type of tubal surgery for hydrosalpinges?
Salpingectomy

A case of salpingectomy

- Large hydrosalpinx visible on ultrasound
- One failed IVF treatment
- Laparoscopic surgery
- Dense adhesions between L tube and bowel and pelvic side wall
- 2 hour operation, salpingectomy
- Day 3, sepsis, bowel leak
- Colostomy, ITU for 1 weeks
Which type of tubal surgery for hydrosalpinges?

- Salpingostomy
- Salpingectomy
- Proximal tubal occlusion / ligation

Gelbaya et al
Fertil Steril 2006, 85;1464

- Retrospective study involving 40 women who had salpingectomy and 25 women who had proximal tubal division
- Prophylactic salpingectomy appears to reduce ovarian response to stimulation
- No difference in pregnancy rate and miscarriage rate
POSSIBLE ADVANTAGES OF PROXIMAL TUBAL OCCLUSION

- Simpler operation than salpingectomy
- ? Less likely to affect blood supply to ovary and therefore ovarian response in IVF treatment cycles

Disadvantages of proximal tubal occlusion

- Pain may get worse
- Risk of recurrent infection and pyosalpinx
- May require further surgery to remove the diseased tube at a later date
- The data on possible benefit is not as robust as that of salpingectomy

RCT : proximal tubal occlusion Vs salpingectomy
Kontoravdis et al, Fertil Steril 2006

<table>
<thead>
<tr>
<th></th>
<th>Ongoing pregnancy rate per transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubal occlusion</td>
<td>37.8%</td>
</tr>
<tr>
<td>(n=45)</td>
<td></td>
</tr>
<tr>
<td>Salpingectomy</td>
<td>48.9%</td>
</tr>
<tr>
<td>(n=47)</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>7.1%</td>
</tr>
<tr>
<td>(n=14)</td>
<td></td>
</tr>
</tbody>
</table>
HYDROSALPINES

GOOD PROGNOSIS

SALPINGOSTOMY

Significant adhesions

Proximal occlusion

POOR PROGNOSIS

SALPINGECTOMY

How can Surgery improve the results of ART

- Intra-uterine pathology
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ENDOMETRIAL SCRATCH -1

- RCT of repeated endometrial biopsies in the cycle immediately preceding IVF treatment significantly increased (~doubled) the implantation, pregnancy and live birth (28%, 67% & 49%) rates in women who had one or more IVF failure compared with control subjects (14%, 30% and 23%) (Barash et al 2003)
ENDOMETRIAL SCRATCH - 2

- Cohort study of repeated endometrial biopsies in the cycle immediately preceding IVF treatment significantly increased the implantation & pregnancy (11% & 30%) rates in 60 women who had more than 4 fresh embryo transfer compared with 57 control subjects (4% & 12%) (Raziel et al 2007)

Endometrial Scratch -3

- RCT
- 115 women with at least two implantation failures
- Endometrial biopsy in the luteal phase of cycle preceding IVF/ICSI

Karimzadeh et al, 2009
Aust NZJ Obstet Gynaecol 49: 677-80

Endometrial scratch

<table>
<thead>
<tr>
<th></th>
<th>Biopsy Gp</th>
<th>Control Gp</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation rate</td>
<td>10.9%</td>
<td>3.4%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>27.1%</td>
<td>8.9%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Karimzadeh et al, 2009
Aust NZJ Obstet Gynaecol 49: 677-80
Summary

Office hysteroscopy performed in the preceding menstrual cycle improves CPR after recurrent implantation failure

WHAT IS RECURRENT IVF FAILURE?

What is Recurrent Implantation Failure?
RECURRENT IMPLANTATION FAILURE

- About 2/3 of centres in UK defined recurrent IVF failure as a failure to achieve a pregnancy after 3 completed fresh IVF-ET cycles (often excluding FER) (Tan et al 2005)
- Failure to achieve a pregnancy after 3 IVF cycles, in which reasonably good embryos were transferred (Margalioth et al 2006)
- Failure to achieve a pregnancy after a total of 10 or more embryos had been transferred to the uterus (Stern et al 2003)

Recurrent IVF Failure
Recurrent Implantation Failure

- How many cycles? How many embryos?
- Should it refer only to those with good quality embryo replaced?
- Age limit?
- Have standard investigations been performed to establish the underlying causes?

RECURRENT IMPLANTATION FAILURE

- Failure to achieve a clinical pregnancy following the transfer of at least four embryos
- in at least 3 fresh or frozen cycles
- in which good quality embryos were transferred
- in women aged less than 40 years
THANKYOU