

Intravaginal Culturing

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Expert-meeting

“Infertility in developing countries: hidden and forbidden desires”
Arusha, December 17, 2007

Historic 1

Over 800 cases of IVC performed by infertility groups around the world (France, Germany, England, USA, Japan,...) have been documented in peer-reviewed journals, demonstrating success rates (average clinical pregnancy rate of 19.7% per cycle) which were comparable to conventional IVF rates (20%) at this time.

Historic 2

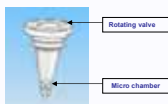
Publication	Location	No. cycles	Clinical Pregnancy Rate
Ranoux, et al., <i>Fertility and Sterility</i> , Vol. 49, No. 4, pp. 654-657, 1988	France	100	20% (per cycle)
Sterzik, et al., <i>Human Reproduction</i> , Vol. 4 Supplement, pp. 83-86, 1989	Germany	22	22.7% (per cycle)
Ranoux, and Seibel, <i>Journal of In Vitro Fertilization and Embryo Transfer</i> , Vol. 7, No. 1, pp. 6-8, 1990	France	100	22% (per retrieval)
Wiegerinck, et al., <i>Ovulation to Implantation</i> , ed. J.H.L. Evers and M.J. Heineman, Elsevier Science Publishers, B. V., pp. 349-351, 1990	Netherlands	55	18.75% (per transfer)
Fresde et al., <i>Wein Med. Wochenschr.</i> , Vol. 140, N° 20, pp. 498-501, 1990	Germany	15	30% (per cycle)
Costoya, et al., <i>Journal of In Vitro Fertilization and Embryo Transfer</i> , Vol. 8, No. 6, pp. 360-361, 1991	Chile	18	14.3% (per transfer)
Taymor, et al., <i>Obstetrics and Gynecology</i> , Vol. 80, No. 5, pp. 888-891, 1992	US	51	10% (per cycle) Natural cycle
Sharma and Hewitt, <i>Bombay Hospital Journal</i> , Vol. 35, No. 2, pp. 155-60, 1993	UK	375	20.4% (per transfer)
Barres, et al., Poster Presentation, Annual Meeting of the American Society for Reproductive Medicine, Cincinnati, Ohio, October 1997	US	106	23% (per transfer)
TOTAL		842	19.7% per cycle

Prototype

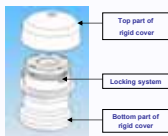
- The IVC Technique was developed to simplify IVF
- The early prototype was difficult to handle
 - Only one sterile opening and closing
 - Overflow of medium during closing → loss of gametes
 - Denuded embryos were difficult to find after incubation under microscope due to a large volume of culture medium (3 ml)
 - Openings of the prototype were reported during its placement and removal from the vaginal cavity → culture medium contamination
- New INVOcell device addresses all these problems



New INVO cell Device



- **Inner Chamber**
 - Rotating valve allows several openings and closings without interposition of air
 - Small orifice of the valve limits changes in pH and prevents loss of gametes
 - Micro chamber collects the embryos and allows their observation directly under microscope



- **Rigid Cover...**
 - Perfect seal protects inner chamber from vaginal secretions and keeps medium sterile
 - The walls of INVOcell are permeable to CO₂
- **Medium:** Complete P- 1 medium with SSS

- **Retention System**

Diaphragm with holes in the membrane maintains the INVOcell device in the vagina with normal flow of vaginal secretions

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IVC: Simplified IVF Procedure

IVC allows IVF in an office setting

- Same indications as conventional IVF
- Mild or no ovarian stimulation (< 10 follicles)
- Retrieval under ultrasound guidance
- INVO fertilization (vaginal incubation)
- Embryo transfer (2 best embryos)

Mild or No Ovarian Stimulation

- **FSH & GnRH antagonist + hCG**

1 to 2 ampoules of FSH every day, antagonist at late follicular phase
Recruitment of 10 follicles or less

- **CCalone, CC & FSH + hCG**

CC 100mg, D3 to D7, or CC 50 mg until hCG administration
FSH 75 IU every day or 150 IU every two days from D6
Recruitment of 5 to 6 follicles

- **Natural cycle & GnRH antagonist + hCG**

Antagonist at day 8 to day 10 to prevent the LH surge
Recruitment of 1 to 2 follicles

Oocyte Retrieval

- **Pre medication ± local anesthesia**

- **Ultrasound guidance**

Using a vaginal probe with a needle guide

- **Follicular puncture through the vaginal wall**



INVO™ Process

In the INVO process prepared sperm, retrieved eggs and P-1 medium with SSS (Serum Substitute Supplement, from Irvine Scientific, CA, US) are combined in the INVOcell. The INVOcell is inserted into the woman's vaginal cavity where it incubates for 3 days. The woman then returns to the doctor's office where the INVOcell is removed and the embryos are observed, loaded into a catheter and transferred into the woman's uterus. The entire INVO procedure takes approximately 3 hours.



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Capital Equipment

- **Rapid hormonal assay instrument to monitor the ovulation**

Hormonal assays performed by local laboratory or loan of an instrument with cost included in the cost of disposables

- **Ultrasound machine with vaginal probe and vacuum pump**

Cost \$ 7,000 to \$ 30,000

- **Laminar flow including warm bench, small incubator and stereomicroscope with video system and bench centrifuge**

Cost \$ 7,000 to \$ 30,000



Disposable Equipment

- **Needle for oocyte retrieval**

Cover probe, tubes for follicular fluid

- **INVO device & retention system**

Petri dishes, tubes, pipettes, slides and gloves

- **Media**

Washing and culture media

- **Embryo transfer catheter**

BioXcell will develop a kit including all the disposable equipment needed to perform INVO



INVOcell Accreditation

- INVOcell device has been ISO 10993 tested (and mouse embryos tested) to assess toxicity and biocompatibility
- Clinical tests have been performed to evaluate the comfort and retention of INVOcell within the vagina
- A clinical trial performed in an infertile population has shown the INVOcell to be a well accepted, non traumatic, effective device with births of normal babies
- BioXcell received certification for ISO 13485
- CE Marking expected in Jan 2008
- FDA 510k approval expected Q2 2009

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Disadvantages of Intravaginal culture system

In the IVC procedure embryos are not checked for polyspermy at 18 hours post insemination:

- A polyspermic embryo with a normal morphology can be transferred to the uterus. Reported risks are:
 - Hydatidiform mole, but hydatidiform mole is essentially related to age, race and diet
 - Most triploids (69 chromosomes) abort spontaneously between 7 and 17 weeks
- A better oocyte maturity obtained by new protocols of ovarian induction and low sperm concentrations used in IVC (10,000 to 30,000 motile spz.) reduced dramatically the risk of polyspermy at fertilization
- A higher rate of miscarriage has not been observed in IVC

Advantages of the IVC Procedure

- IVC does not require expensive and complex capital equipment
- As the gametes and embryos are not stored in the office, air filtration system, CO₂ supplementation, alarm system, embryologist on call are not necessary
- IVC can be available everywhere in a physician office
- IVC procedure does not require the same expertise from the operator and same overhead as in an IVF center
- The simplified procedure using IVC associated with a mild ovarian stimulation decreases the time of the operators performing this infertility treatment
- IVC is a simple, effective and less expensive IVF alternative (1/3 to half the cost of an IVF treatment) that can be performed almost everywhere

Conclusion

- Into countries where the infertile population cannot access conventional IVF for economic or geographic reasons
- To IVF Centers as an alternative treatment for their infertile population they could not reach before
- To Ob/Gyn groups where IVF centers are not present
