

INVOcell™ INSTRUCTIONS FOR USE

INDICATIONS FOR USE

The INVOcell™ Intravaginal Culture System consists of the following components:

The INVOcell Culture Device is indicated for use in preparing, holding, and transferring human gametes or embryos during In Vitro Fertilization/Intravaginal Culture (IVF/IVC) and Intra-Cytoplasmic Sperm Injection Fertilization/Intravaginal Culture (ICSI/IVC) procedures. The INVOcell Culture Device is indicated for use with the INVOcell Retention Device. The INVOcell Culture Device is not indicated for incubation periods exceeding 72h.

The INVOcell Retention Device is indicated for use with the INVOcell Culture Device to aid in retention of the INVOcell Culture Device in the vaginal cavity during the incubation period. The INVOcell Retention Device is not indicated for use exceeding 72 hours.

Note: Federal law (USA) restricts this device to sale only by or on the order of a physician.

CONTRAINDICATIONS

The INVOcell Intravaginal Culture System should not be used in patients with the inability to tolerate the placement or wearing of the INVOcell Culture Device or INVOcell Retention Device.

WARNINGS

The INVOcell Culture Device and INVOcell

Retention Device are single use only, do not reuse.

Do not use if product or package appears damaged. If the packaging is damaged, the product may no longer be sterile.

Do not use the INVOcell Culture Device in patients with demonstrated hypersensitivity to medical grade silicone or polystyrene.

The INVOcell Intravaginal Culture System should not be used in patients with a severe case of vaginitis.

The INVOcell Intravaginal Culture System should not be used in patients with a history of toxic shock syndrome.

Before using the INVOcell Intravaginal Culture System, patients should be evaluated for any recent pelvic surgery to assure it will not affect the intravaginal culture procedure.

Do not incubate gametes and/or embryos in the Intravaginal Culture Device beyond 72 hours.

Proper handling is extremely important to the safe and effective use of the INVOcell Intravaginal Culture Device. Do not begin clinical use of the INVOcell Intravaginal Culture System without establishing competency by reading and practicing these instructions for use.

INVOcell Intravaginal Culture System should be handled under aseptic conditions at all times.

After the INVOcell Intravaginal Culture Device has contacted the vaginal environment, the surfaces of the device, including those of the inner vessel, should be handled as if contaminated by vaginal flora.

Utilize a legally-marketed ART culture medium that will support continued embryonic development for up to 72 hours.

Culture media utilized with the INVOcell system **MUST** contain antibiotics to mitigate the risk of contamination of media in the inner chamber.

Culture media utilized with the INVOcell system should have phenol red to aid in the determination of acceptable pH maintenance.

Using the INVOcell Culture Device and INVOcell Retention Device, embryo development is first evaluated at the end of the incubation period at 72 hours post fertilization. Any abnormalities that would have been detected at an earlier stage (pro-nuclei stage) may no longer be apparent when the embryos are evaluated for transfer. As a result, there may be an increased risk that an abnormal embryo could be transferred to the uterus compared to traditional IVF.

Do not use a 0-200 μ L tip to add oocytes to the INVOcell Culture Device as the oocytes may stick in the tip and/or become damaged.

Ensure that the embryo retrieval catheter

complies with the list of catheters and the tip outer diameter requirements listed in the accessory section on page 4.

PRECAUTIONS

INVOcell procedures should only be conducted by physicians with expertise in assisted reproductive technology and techniques including oocyte retrieval, clinical embryology, and embryo transfer, and with access to all equipment listed in the Required Accessories section.

It is recommended that the INVOcell Intravaginal Culture system be utilized with a mild ovarian stimulation protocol.

It is recommended to use the Fisherbrand™ Block (88-860-105_24 x 13mm diameter) or equivalent to hold the inner chamber of the INVOcell Culture Device for maintaining the culture device temperature during loading and embryo retrieval procedures. The block is non-sterile and must be cleaned and disinfected between uses. It is recommended to follow the Fisherbrand™ or equivalent block manufacturer's cleaning and disinfecting process.

The recommended upper limit on number of oocytes or ICSI fertilized embryos to be placed in the INVOcell Culture Device is seven. Verify that the outer rigid shell and inner chamber of the INVOcell Culture Device are correctly locked before placement of the INVOcell Culture Device and the INVOcell Retention Device in the vaginal cavity.

Advise the patient to avoid the following activities while the INVOcell Culture Device

and the INVOcell Retention Device are in the vaginal cavity: sexual intercourse, strenuous physical activity, swimming, bathing in a tub (a shower is permissible), use of a douche, sauna, or any activity that may alter the temperature of the vaginal cavity.

Instruct the patient to contact the physician if any of the following are observed: discomfort, bleeding, movement of the INVOcell Culture Device or INVOcell Retention Device, unusual vaginal secretions, or vaginal odor.

Instruct the patient not to remove the INVOcell Culture Device and the INVOcell Retention Device from the vaginal cavity and to avoid manipulation of the INVOcell Culture Device and the INVOcell Retention Device.

Provide the patient with instructions for replacement of the INVOcell Culture Device and the INVOcell Retention Device in the event it moves from its original position.

If obvious contamination of culture medium is observed when the INVOcell Culture Device is removed from the vaginal cavity the embryos should be discarded.

The working environment in the laboratory should be at a minimum of 22°C to maintain the culture media temperature in the block at or above 34°C for 10 minutes during the loading process and embryo aspiration process.

DEVICE DESCRIPTION

The INVOcell Culture Device is a three-part assembly (see Figures 1 and 2) enclosed in two separate packages.

FIGURE 1: Inner Vessel

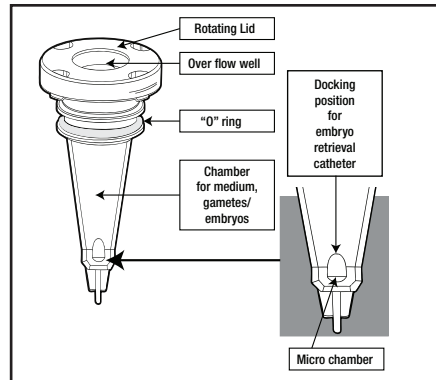
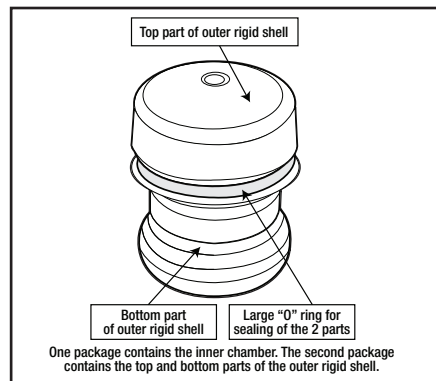


FIGURE 2: Outer Rigid Shell for Cell Culture Container

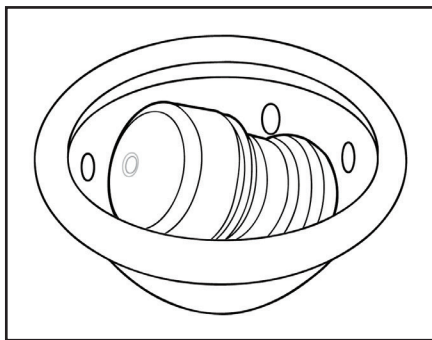


The inner vessel holds culture medium, eggs and sperm, or ICSI fertilized embryos. In an INVOcell procedure, the inner vessel is placed into the outer rigid shell, which provides additional resistance to contamination.

Following the loading of gametes or embryos, the INVOcell Culture Device is assembled and placed in the vaginal cavity for 72 hours to allow for embryo development.

The INVOcell Retention Device is a single-use, device that includes holes to allow for natural drainage of vaginal fluids (see Figure 3). The retention device is placed into the vaginal cavity with the INVOcell Culture Device to ensure that the INVOcell Culture Device is retained in the vaginal cavity for 72 hours. The retention device comes in a single size: 70mm.

FIGURE 3: INVOcell Retention Device Cradling the INVOcell Culture Device



Prior to loading or retrieval procedures, the blocks must be pre-warmed in an incubator. A period of 200 minutes is required to heat the block from 30°C to 37°C in an incubator. During use with the INVOcell culture device, a block that started at 37°C can maintain a temperature at or above 34°C for 10 minutes in a room at 22°C (72°F). To reheat a block from 34°C to 37°C in an incubator, a period of at least 80 minutes is necessary. Due to the amount of time required to heat the blocks, it is recommended that the blocks be preheated well in advance of an INVOcell culture device removal procedure, and that backup blocks be available.

MATERIALS

The inner chamber of the INVOcell Culture Device is made of polystyrene and synthetic rubber latex /thermoplastic elastomer (TPE) with a silicone o-ring. The outer rigid shell of the INVOcell Culture Device is made of polystyrene with a large silicone o-ring.

The INVOcell Retention Device is made of medical grade silicone.

Non-Pyrogenic:

The INVOcell Culture Device is endotoxin tested by LAL yielding no more than 20 EU/device.

Non-Embryo Toxic:

The INVOcell Culture Device (inner chamber) has been tested for embryotoxicity yielding at least 80% of 2-cell mouse embryos reaching the blastocyst stage.

REQUIRED ACCESSORIES

The following equipment and supplies (or equivalent) are required for use of the INVOcell Culture System:

- Laminar flow workstation.
- 37°C desktop incubator with 5% CO₂.
- Embryo freezing and storage equipment
- Stereomicroscope
- Bench centrifuge
- Adjustable volume pipettes from 5 –1000 µL; and sterile pipette tips.
- Embryo medium approved to support embryo development for 72 hours containing antibiotics and phenol red
- Embryo retrieval catheter with an outer diameter between 1.0mm and 1.85 mm.
- 1 mL syringe.
- Powder-free gloves.

- Fisherbrand™ Blocks (88-860-105_24 x 13mm diameter) or equivalent (2).
- INVOcell Retention Device for retaining the INVOcell Culture Device in the vaginal cavity.
- 5.25% Sodium Hypochlorite solution
- Clean wipes

INSTRUCTIONS FOR USE

Standard INVO procedure is below. Clinical Reference Guide is provided separately (P-018).

Store the retention device at room temperature below 25°C (77°F), away from moisture and direct heat. Do not use after the expiration date.

Preparation of the INVOcell Culture Device:

When the INVOcell Culture Device is removed from the pouches, the two parts should be placed in a laminar flow hood for loading the culture media and gametes.

Pre-warm the Following in a 37°C Incubator for at Least 1 hour Prior to Use:

- Unopened package (1 of 2) containing the inner chamber of the INVOcell Culture Device.
- Unopened package (2 of 2) the outer rigid shell of the INVOcell Culture Device.
- Unopened bottle of cell culture medium.

Pre-warm blocks for at least 3 hours prior to use. It is recommended to have a second pre-warmed block ready at 37°C.

Note: Do not use an incubator that is currently storing gametes for IVF to heat outer pouches of the INVOcell Culture Device

or the block, as these components are not sterile.

Open the pre-warmed package (1 of 2) containing the inner chamber of the INVOcell Culture Device. Keep the outer rigid shell of the INVOcell Culture Device in its package at 37°C. Place the closed inner chamber in the pre-warmed block.

Note: The procedure should be performed in an environment with a room temperature of at least 22°C. In these conditions, the block will maintain a sufficient temperature ($\geq 34^\circ\text{C}$) for at least 10 minutes.

The inner chamber is packaged in the closed position. Turn the lid of the inner chamber counter clockwise to open. Rinse the inner chamber with 1 mL pre-warmed culture medium using an adjustable volume pipette to add and remove medium through the circular opening in the lid (**see Figure 4 and Figure 5**).

FIGURE 4: Inner Chamber Closed (a) and Open (b) Positions

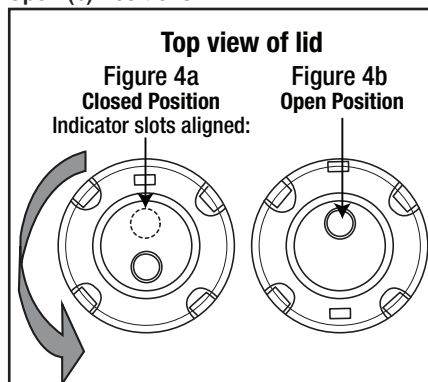
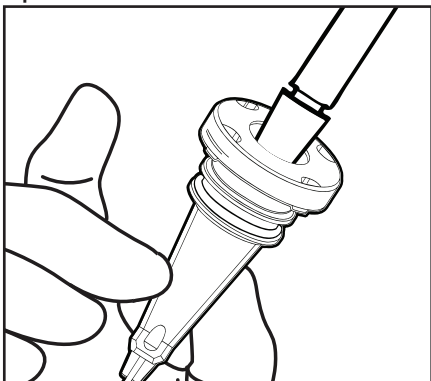


FIGURE 5: Filling the Inner Chamber with a Pipette filled with Culture



Using a sterile glass pipette or a pipette with a thin plastic tip, fill entirely the inner chamber with 1.08 mL pre-warmed culture medium.

Loading Sperm and Oocytes for IVF/IVC:

Using an adjustable volume pipette with a 0-200 μL tip, transfer 30,000 motile sperm into the middle of the inner chamber.

Using a glass pipette or an adjustable volume pipette with a 250-1000 μL tip, transfer no more than 7 oocytes. The added volume for the transfer of the gametes should not generally exceed 50 μL .

Loading ICSI Fertilized Embryos for ICSI/IVC:

ICSI should be performed per standard ICSI laboratory procedures where sperm is injected into the oocyte to obtain fertilization.

Using a glass pipette or an adjustable volume pipette with a 250-1000 μL tip, transfer no more than 7 ICSI embryos. The added volume should not exceed 50 μL .

Closing the Inner Chamber:

Using a pipette eliminate any trapped air bubbles that may have been created by the transfer of the gametes or ICSI-fertilized embryos.

Close the inner chamber by rotating the lid clockwise. Check to make sure that the inner vessel is completely closed prior to proceeding.

Remove any cell culture medium remaining in the overflow well area above the lid with a pipette.

Outer Rigid Shell Installation:

Open the pre-warmed package (2 of 2) containing the outer rigid shell top and bottom.

Open the rigid outer shell and pull out the patient label and write the patient's name or unique identifier on the label. Place the label back into the outer rigid shell.

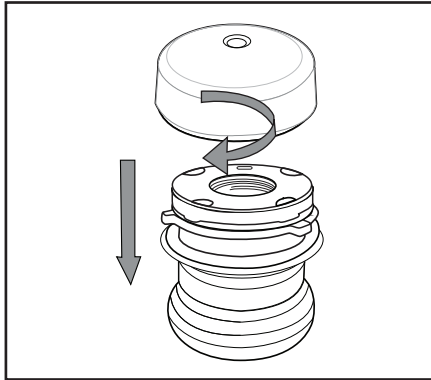
Caution: Do not touch the top surface of the rotating valve of the inner chamber of INVOcell Culture Device during installation into the outer rigid shell to reduce the risk of contamination of media within the inner chamber.

Carefully introduce the inner chamber into the outer rigid shell bottom. Verify that the small tip at the lower extremity of the inner chamber is positioned in the small cylinder feature located inside the bottom of the outer rigid shell.

Close the outer rigid shell by pushing the top part down on the large o-ring, making sure the three tabs of the bottom part are

engaged in the corresponding holes of the top part. While maintaining pressure, rotate the top part clockwise to lock the outer rigid shell (see Figure 6).

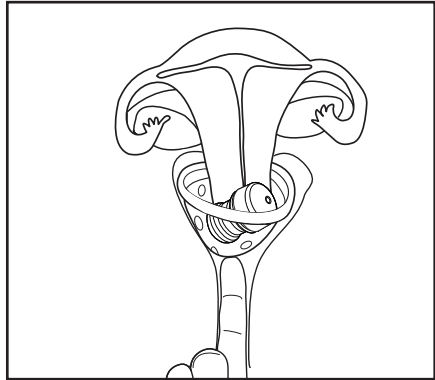
FIGURE 6: Placement of the INVOcell Culture Device and the INVOcell Retention Device in the Vagina



Caution: Verify that the outer rigid shell of the INVOcell Culture Device is correctly locked before placement of the INVOcell Culture Device and the INVOcell Retention Device in the vaginal cavity. When locked, the top of the outer shell should not be able to rotate clockwise.

The INVOcell Culture Device should then be placed immediately in the vaginal cavity as instructed below.

FIGURE 7: Intravaginal



Place the INVOcell Culture Device in the pocket of the INVOcell Retention Device. Rinse the loaded, fully assembled INVOcell Culture Device and INVOcell Retention Device with pre-warmed (37°C) water or saline solution and insert the devices longitudinally in the vagina. Push deep into the vaginal channel and then Rotate 90 degrees in the horizontal plane to position in the posterior fornix behind the cervix (see Figure 7).

Incubate the INVOcell Culture Device in the patient's vagina for 72 hours.

Warning: Do not incubate longer than 72 hours.

Caution: Instruct the patient not to remove the INVOcell Culture Device and INVOcell Retention Device from the vaginal cavity and to avoid manipulation of the INVOcell.

Caution: Instruct the patient to avoid the following activities while the INVOcell Culture Device and the INVOcell Retention Device is in the vaginal cavity: sexual intercourse, strenuous physical activity, swimming, bath-

ing in a tub (a shower is permissible), sauna, use of a douche, or any activity that may alter the temperature of the vaginal cavity.

Caution: Instruct the patient to contact the physician if any discomfort is felt, bleeding occurs, device feels as though it has moved, or any unusual vaginal secretions or vaginal odor occurs.

In the event the patient cannot tolerate the wearing of the device once placed in the vaginal cavity, remove the device per removal section below and place the block with the inner vessel and gametes into a 5% CO₂ incubator for the remaining time of the 72 hours. Note that the device effectiveness after incubation in a standard incubator has not been evaluated in clinical studies.

Caution: Instruct the patient to push the INVOcell Culture Device and retention device manually up into the vaginal cavity if the patient feels as though the devices are slipping out of place. If the patient experiences slippage, she should call her physician (see FIGURE 7).

Caution: Instruct the patient on how to replace the INVOcell Culture Device and Retention Device in the vagina if the devices dislodge from the vaginal cavity. If this occurs, the patient should rinse the Culture Device in warm water and manually insert it back into the vagina as deep as possible and call her physician immediately for instruction. Her physician may instruct her to replace the retention device or request her return to the physician's office for placement of a new retention device.

Removal of the INVOcell Culture Device and INVOcell Retention Device:

Pre-warm the Following in a 37°C Incubator for at Least 1 hour Prior to Removal of the INVOcell Culture Device:

- Clean saline solution for rinsing of the INVOcell Culture Device exterior
- Fisherbrand™ Block (88-860-105_24 x 13mm diameter) or equivalent

Prior to removal of the INVOcell culture device from the vagina, blocks should be pre-warmed in an incubator. Be sure that at least one block is heated to 37°C. It takes at least 200 minutes to heat the block from 30°C to 37°C, and even longer if the block has cooled to room temperature. It is recommended to have an additional block heated and ready in case the extraction procedure exceeds 10 minutes.

Assure that a block is heated according to the instructions above and remove the block from the incubator upon retrieval of the device from the vaginal cavity.

Caution: Record the time the block was removed from the incubator. The block only holds the temperature of the contents of the inner vessel at >34°C for 10 minutes once removed from the incubator. If the contents of the device are not transferred to an embryo culture dish by 10 minutes, place the block with the inner vessel back into the incubator or take another heated block from the incubator and transfer the inner vessel to the newly heated block.

Warning: After the INVOcell Intravaginal Culture Device has contacted the vaginal

environment, the surfaces of the device, including those of the inner vessel, should be handled as if contaminated by vaginal flora.

After incubation, remove the INVOcell Culture Device and the INVOcell Retention Device from the posterior fornix behind the cervix by pulling on the outside ring of Retention Device; the INVOcell Culture Device will be removed with the INVOcell Retention Device.

Rinse the INVOcell Culture Device with pre-warmed saline solution and wipe with clean gauze to remove excess vaginal secretions. Holding the outer rigid shell upright, open it by turning the top part counter clockwise. Discard the outer rigid shell top.

Change to new sterile gloves.

Carefully remove the inner chamber from the outer rigid shell bottom without touching the outside of the outer rigid shell to keep the inner chamber sterile while transferring to the block. Discard the outer rigid shell.

Caution: If there are signs of possible contamination of the outer surface of the inner vessel, flush the outer vessel with warm saline and dry with a lint free cloth prior to placing it in the warming block.

Change gloves before proceeding to the next step.

In the event that the embryo assessment and transfer cannot be performed immediately following removal of the device, place the patient name or identifier label on the block, place the inner vessel and the block into the incubator until the transfer can be performed.

Storage in the incubator should be as short as possible.

Visually check the inner chamber for any signs of leakage or contamination, such as a change in phenol red or turbidity.

Caution: If obvious contamination of culture medium is observed, the embryos should be discarded.

Embryo Aspiration, Selection and Transfer:

Note: This process should be performed in a laminar flow hood.

Set up a catheter for loading the embryos.

Hold the inner chamber so it can be seen under the microscope.
Count the number of embryos seen in the inner chamber.

Turn the rotating valve of the inner chamber to the open position.
Aspirate the total contents of the inner chamber into the catheter.

Transfer contents of the catheter into an embryo culture dish.

Count the embryos to ensure that all embryos have been transferred. If not, locate the remaining embryos under the microscope, aspirate the remaining embryos from the INVOcell Culture Device, and place them in the culture dish.

The embryologist should perform embryo assessment. The number of embryos resulting from incubation should be compared to the number of oocytes placed in the inner chamber and differences noted. Any embryos not transferred should be managed per standard laboratory operating procedures.

Embryo transfer should be performed per the physician's protocol.

Cleaning and Reprocessing of Reusable Components:

The INVOcell Culture Device is provided sterile by radiation sterilization according to manufacturing procedures that have been validated to meet a sterility assurance level (SAL) of 10⁻⁶.

The INVOcell Retention Device is provided non-sterile.

Note: The recommended Fisherbrand™ Block (88-860-105_24 x 13mm diameter) or equivalent block is non-sterile. The block must be cleaned and disinfected between uses. It is recommended to follow the Fisherbrand™ or equivalent block manufacturer's cleaning and disinfecting process.

OUTCOMES OF INITIAL INVO CLINICAL USE

The outcomes of 450 IVC cycles performed during clinical use in four centers outside of the United States (Columbia, Bolivia, Brazil and Peru) is summarized in Table 1.

TABLE 1		
	IVC/IVF	IVC/ICSI
Cycles	330	120
Embryo transfers	308 (93% of cycles)	113 (94% of cycles)
Live births total* Live births (survivors)**	78 (25% of transfers) 76 (25% of transfers)	29 (26% of transfers) 28 (25% of transfers)
Live born babies Live born babies (surviving)	98 94	34 33

*Not included are 6 pregnancies with unknown outcomes, these pregnancies were 4 singles and 2 twins.

**Four IVC/IVF babies died after delivery, one after surgery for intestinal occlusion with no genetic abnormality detected and 3 babies from a triplet delivery at 20 weeks.

One twin IVC/IVF baby from a 39 years old patient had down syndrome. One IVC/ICSI baby died due to major bone malformations and cardiopathy highly suggestive of genetic anomalies. Another IVC/ICSI premature baby born at 30 weeks had congenital scoliosis.

Table 2 below provides effectiveness indicators such as clinical pregnancy rate, miscarriage rate, multiple pregnancy rate, and birth rates resulting from use of the INVOcell device.

TABLE 2	
	INVO cycles (IVF + ICSI)
Cycles	450
Clinical Pregnancies	146
Clinical Pregnancy Rate	32.4%
Miscarriage Rate	22.6%
Multiple Pregnancy Rate	15.1%
Birth Rate	23.8%
Multiple Birth Rate	17.8%
Triplet Births	6
Twin Births	13
Births from Singleton Pregnancies	88
Triplet Pre-term Births (%)	6 (100%)
Twin Pre-term Births	7 (53.8%)
Singleton Pre-term Births from Single Pregnancies	0
Pre-term Birth Rate	21.4%

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