Fertility Preservation in Women with Hereditary Gynecologic Cancer
(유전성 부인암환자에서 가임력 보존)

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Hereditary Gynecologic Cancer Syndromes (HGCS)

Hereditary Cancer Syndrome (HCS)

- 하나 이상의 **pathogenic germline variant**에 의해 발생
- 대부분 **autosomal dominant inheritance**
- 전체 암의 약 **5–10%**
- 현재까지 50개 이상의 HCS가 알려져 있음
- 유전자 검사 기술의 발전으로 진단되는 환자 지속 증가

Major Hereditary Gynecologic Cancer Syndromes (HGCS)

Syndrome	Major Gynecologic Malignancies
Hereditary Breast and Ovarian Cancer (HBOC)	Ovarian / Fallopian tube / Peritoneal cancer
Lynch Syndrome (LS)	Endometrial / Ovarian cancer
Cowden Syndrome	Endometrial cancer
Peutz–Jeghers Syndrome (PJS)	Cervical adenocarcinoma
Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)	Uterine leiomyoma / Renal cell carcinoma

Why Does Fertility Preservation Matter in HGCS?

Hereditary cancer predisposition → Cancer prevention vs. Risk-reducing surgery → Loss of reproductive function → Fertility preservation

Sporadic Cancer



Trigger: Cancer diagnosis.

Threat to Fertility: Chemotherapy, pelvic radiation, or radical therapeutic surgery.

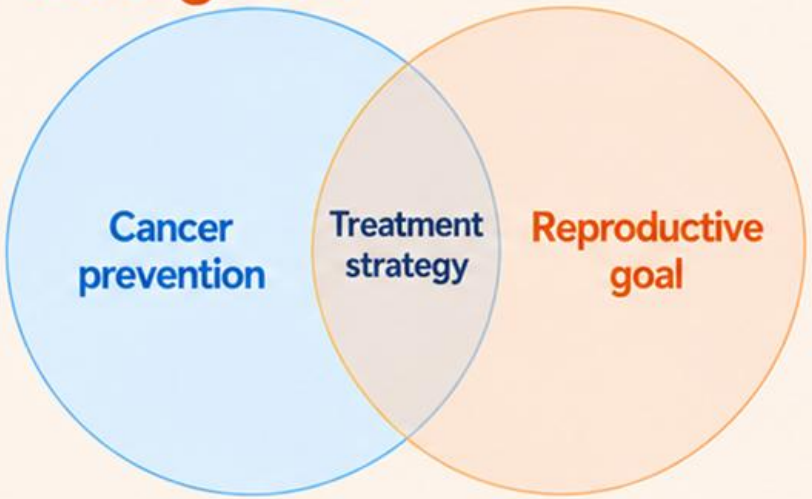
Hereditary Cancer



Trigger: Germline pathogenic variant identification (often while healthy).

Threat to Fertility: The preventative measures themselves.

Plan together

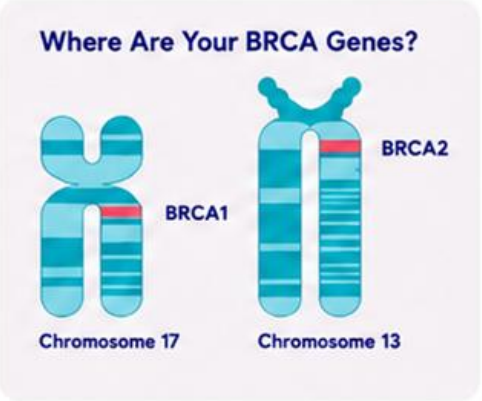


Hereditary Breast and Ovarian Cancer (HBOC)

- **BRCA1 / BRCA2 pathogenic germline variants**

  → Increased risk of **multiple cancers**

- **Breast cancer · Ovarian cancer · Pancreatic cancer · Prostate cancer**



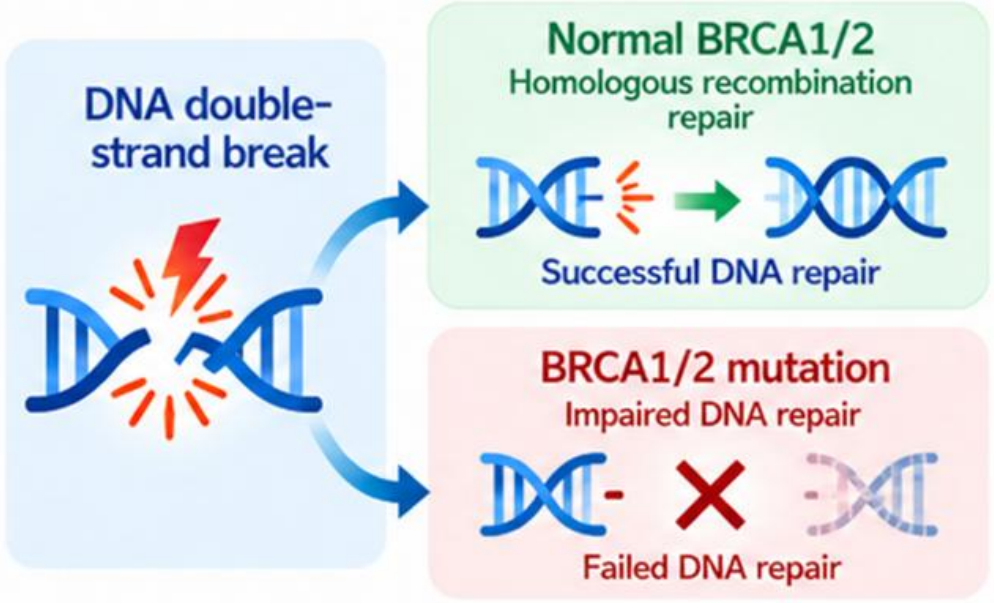
- **Lifetime Cancer Risk (up to age 80)**

	BRCA1	BRCA2
Breast cancer	72%	69%
Ovarian cancer	44%	17%

- **BRCA-associated Ovarian Cancer**
  - Predominantly **High-Grade Serous Carcinoma (HGSC)**
  - **BRCA1 carriers** have a higher ovarian cancer risk than BRCA2 carriers

BRCA Mutation & Ovarian Reserve

BRCA1/2 mutation → Impaired DNA double-strand break repair → Oocyte apoptosis / follicular depletion → Ovarian reserve ↓



Human evidence

- **AMH:** Inconsistent
- **AFC:** Inconsistent
- **Ovarian stimulation response:** Inconsistent
- **BRCA1:** Possible lower ovarian reserve

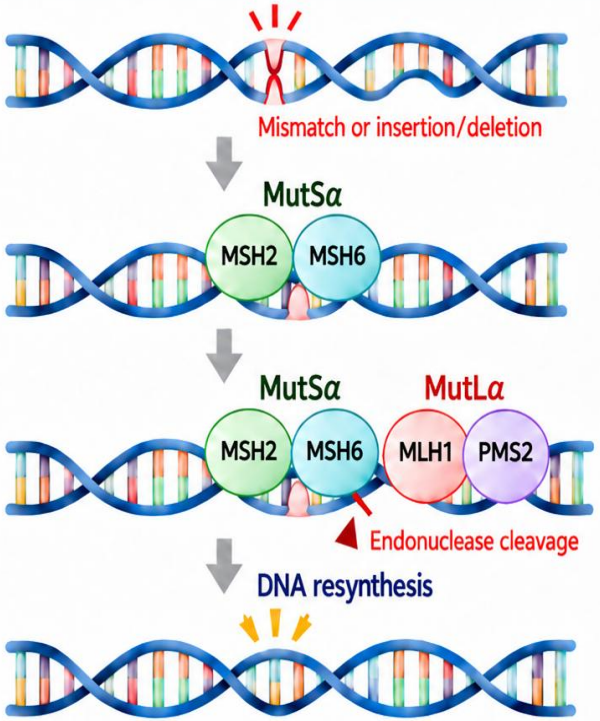
Outcome	BRCA1-m BC	BRCA1-negative BC
AMH (ng/mL)	1.2	4.5
Mature oocyte	3.1	7.1

Corrado G, et al. Int J Gynecol Cancer. 2021;31:332–338.

AMH, Anti-Müllerian Hormone; AFC, Antral Follicle Count; BC, Breast Cancer

Lynch Syndrome (LS)

DNA mismatch repair (MMR): 복제 중 발생한 염기 불일치 및 작은 삽입/결실 오류를 교정하는 기전



MMR deficiency

↓

Unrepaired replication errors

↓

Mutation accumulation + MSI
(Microsatellite Instability)

↓

Increased cancer risk

Genetic Basis

- **Autosomal dominant** inheritance
- **MMR genes**: MLH1 · MSH2 · MSH6 · PMS2
- Defective DNA mismatch repair → Cancer risk ↑

Major Cancer Risks

- Colorectal · Endometrial · Ovarian · other cancers
- EM cancer: **lifetime risk up to ~60%**
- OV cancer: **lifetime risk up to ~24%**

Gene-Specific Risk

- Cancer risk varies by MMR gene
- **MLH1 / MSH2 / MSH6**: risk rises markedly from ~40 yr
- **PMS2**: lower risk and later onset

Gynecologic Cancer in LS

LS-Associated Endometrial Cancer (EC)

- **Earlier onset** than sporadic EC
- Predominantly **endometrioid histology**
- Other high-grade histologies (serous, clear) may occur

Why It Matters for Fertility

- **Early cancer onset** → Cancer treatment or RRS (Risk-reducing hysterectomy ± BSO) → Fertility loss
- **No clear evidence** of direct **ovarian reserve** impairment in LS

Early reproductive counseling is essential before treatment or RRS.

EC, Endometrial Cancer; LS, Lynch Syndrome; RRS, Risk Reducing Surgery

Fertility-Sparing Treatment for Early EC in LS

Conservative Tx. in Early EC

- Oral progestins / LNG-IUD in selected patients

Clinical Evidence: MMRd tumor

Outcome	MMRd-EC	MMRp/NSMP-EC
Complete response	48.8 %	78.4 %
Recurrence	42.8 %	18.4 %

- Lower progestin response and higher recurrence

Considerations in LS-Associated Early EC

- MMRd tumors may respond less to progestins.
- MMRd phenotype does not necessarily indicate LS.
- LS-specific evidence: Limited.
- Careful counselling: Persistence and Recurrence.
- Close surveillance:
- Definitive surgery after child bearing.

Ferrari FA, et al. Int J Gynecol Cancer. 2025;35:100016./Corrado G, et al. Int J Gynecol Cancer. 2021;31:332–338.

MMRd. Mismatch Repair deficiency; EC, Endometrial Cancer; LS, Lynch Syndrome; LNG-IUD, levonorgestrel-releasing intrauterine device; RRS, Risk Reducing Surgery

Risk Assessment for HGCS

Clinical Clues

- Early-onset cancer (age <50)
- Multiple primary cancers
- Strong family history

Tumor Clues

- Triple-negative BC + OV cancer → HBOC
- MMR-d / MSI-H EC + colorectal cancer → LS
- Characteristic histologic / molecular features

Suspected HGCS → **Genetic counseling** → **Germline testing (NGS / multigene panel)** → **Clinical management**

- Surveillance
- RRS
- Reproductive counseling

Why Early Identification Matters

- Enables gene-specific cancer surveillance and prevention
- Individualized RRS timing based on reproductive goals
- Early fertility preservation (FP) counseling

BC, Breast Cancer; LS, Lynch Syndrome; EC, Endometrial Cancer; NGS, Next Generation Sequencing, RRS, Risk Reducing Surgery

Risk-Reducing Surgery & Timing

BRCA1 / BRCA2: RRSO

- BRCA1: **Age 35–40 years**
- BRCA2: **Age 40–45 years**

- OV cancer risk ↓
- Surgical menopause

Lynch Syndrome: Hysterectomy ± BSO

- Timing based on gene-specific risk and reproductive goals
  - MLH1 / MSH2 / MSH6: **After childbearing or age 40**
  - PMS2: **After childbearing or age 50**

- EM / OV cancer risk ↓
- Hysterectomy: Loss of gestational capacity
- BSO: Loss of ovarian function

Whenever oncologically appropriate, individualized RRS timing based on cancer risk and reproductive goal.

RRSO, Risk Reducing Salpingo-Oophorectomy; BSO, Both Salpingo-Oophorectomy; RRS, Risk Reducing Surgery

Angelina Jolie Underwent Surgery to Have Ovaries Removed

The procedure was motivated by a family history of cancer.



Angelina Jolie Details Ovarian Surgery Hollywood actress had preventative surgery to avoid cancer risks.

By DAN GOOD
March 24, 2015, 4:02 PM

Follow ABC News on Google Share

— -- Angelina Jolie underwent preventative surgery to have her ovaries and Fallopian tubes removed because of cancer fears, she wrote in a New York Times op-ed.

The procedure, laparoscopic bilateral salpingo-oophorectomy, was motivated by a family history of ovarian cancer. A small benign tumor was found on one ovary, but no

Jolie's mother, grandmother and aunt died from cancer.

"Regardless of the hormone replacements I'm taking, I am now in menopause," she wrote. "I will not be able to have any more children, and I expect some physical changes. But I feel at ease with whatever will come, not because I am strong but because this is a part of life. It is nothing to be feared."

Previously, Jolie underwent preventative double mastectomy after a blood test showed a mutation in the BRCA1 gene.

In her op-ed, titled "Diary of a Surgery," Jolie, 39, stated that tests showed elevated risks for cancer, forcing her to move up the surgery.



- Mother, grandmother and aunt **died from cancer** (ovarian cancer).
- **BRCA1** mutation
- **2013 (age 37): Risk-reducing mastectomy (RRM)**
- **2015 (age 39): Risk-reducing salpingo-oophorectomy (RRSO)**

Fertility Preservation Before RRS

1. Embryo Cryopreservation



2. Oocyte Cryopreservation



3. Ovarian Tissue Cryopreservation



4. Other Options

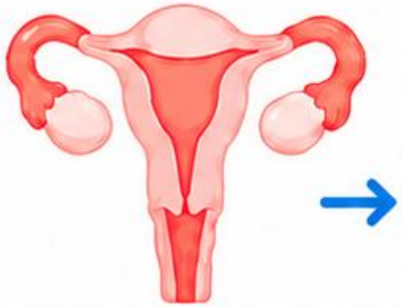


FP counseling should occur BEFORE cancer treatment or RRS whenever possible.

ASCO Fertility Preservation Guideline Update, 2025.

Embryo & Oocyte Cryopreservation

Before FP



Ovarian reserve assessment (AMH / AFC)

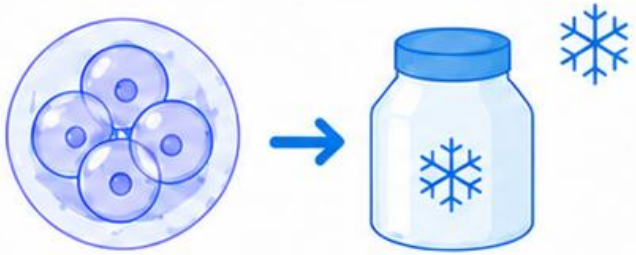
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Predict ovarian response

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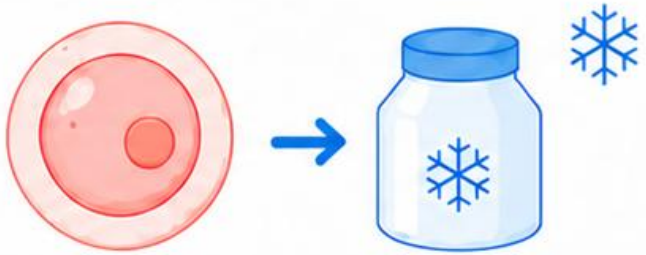
Individualized FP strategy

Embryo Cryopreservation



- Established FP method
- Requires **ovarian stimulation**
- Requires **sperm for fertilization**
- Clinical pregnancy rate ~40%
- Live birth rate ~33%

Oocyte Cryopreservation



- Established FP method
- Requires **ovarian stimulation**
- **No sperm** required
- Suitable for young HGCS carriers
- Multiple retrieval cycles possible

Age matters: earlier fertility preservation provides a greater opportunity for future pregnancy.

FP, Fertility preservation; AMH, Anti-Müllerian Hormone; AFC, Antral Follicle Count; HGCS, Hereditary Gynecologic Cancer Syndrome

Is Ovarian Stimulation Safe?

Breast Cancer

- Letrozole + gonadotropins **minimize estrogen exposure** in ER-positive disease.
- **Comparable oocyte / embryo yield** with letrozole-based protocols.
- **No adverse survival signal** in available studies.

BRCA Mutation Carriers

- IVF was **not associated** with increased ovarian cancer risk.
  (OR 0.33, 95% CI 0.04–3.30; p=0.35)
- **No significant association** with specific fertility medications.

Current evidence is reassuring, but BRCA-specific safety data remain limited.

Gronwald J, et al. Fertil Steril. 2016;105:781–785. | Corrado G, et al. Int J Gynecol Cancer. 2021;31:332–338.

Ovarian Tissue Cryopreservation (OTC)

OTC



Ovarian tissue retrieval
↓
Cryopreservation
↓
Future autotransplantation
↓
Restoration of ovarian function & fertility

Who May Benefit?

- Established FP method
- Adolescents / prepubertal girls
- Ovarian stimulation not feasible (no ovarian stimulation required)
- Urgent cancer treatment
- Unable to undergo oocyte / embryo cryopreservation

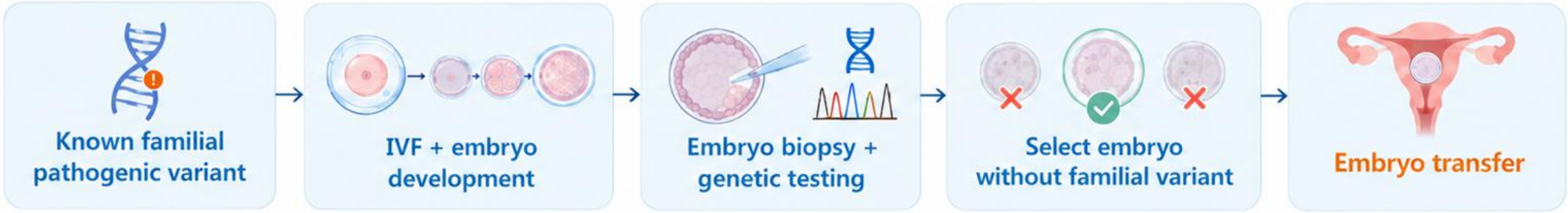
Outcomes & Limitations

- Endocrine recovery: **>95%**
- Pregnancy rate: **~40%**
- Follicle loss during freezing / revascularization
- **Risk of malignant cell reimplantation**

OTC is an established FP option when oocyte or embryo cryopreservation is not feasible.

PGT-M in HGCS

PGT-M: Preimplantation Genetic Testing for Monogenic disorders



Where It Applies

- BRCA1 / BRCA2
- Lynch syndrome (MMR genes)
- Other hereditary cancer syndromes with known pathogenic variants

Clinical Role & Considerations

- Reduces transmission of a familial pathogenic variant
- Reproductive option, not cancer treatment
- Requires genetic and reproductive counseling
- **Subject to local regulations and eligibility criteria**

판 판례 연 연혁 행 위임행정규칙 규 규제 생 생활법령 한 한눈보기

보건복지부 보도참고자료 대체불가 대한민국

보도시점 배포 후 즉시 사용 배포 2026. 10. 15.(목)

배아 또는 태아 대상 유전자검사 가능 유전질환 7개 추가 선정

- 연골모발형성저하증, 피어슨 증후군 등 총 264개 질환으로 확대 -

보건복지부(장관 정은경)는 10월 15일(목) 배아 또는 태아 대상 유전자검사가 가능한 유전질환 7개*를 추가로 선정하고, 이를 포함한 전체 264개 유전질환을 보건복지부 누리집(https://www.mohw.go.kr)**에 공고했다.

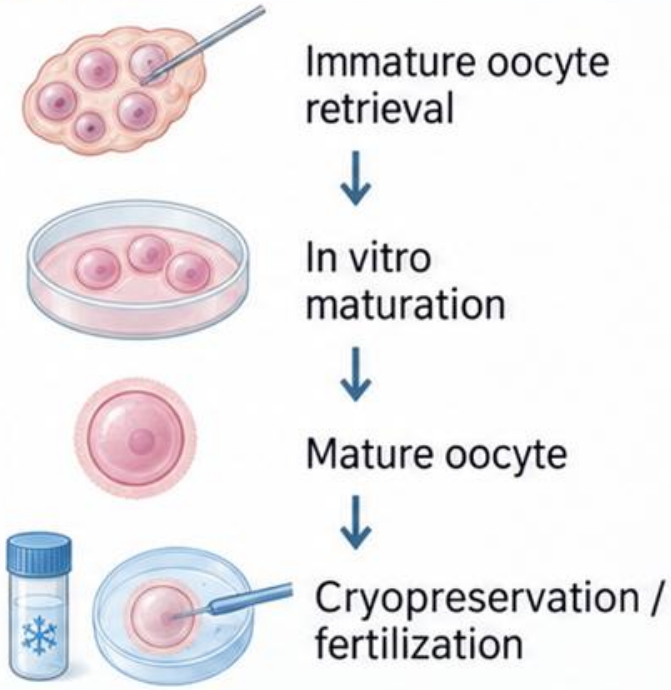
카테고리	유전질환명
	선천성다발성관절구축증 (Arthrogryposis multiplex congenita) ※ 해당 분야 전문의의 판단에 따라 유전적 원인이 밝혀진 유형에 대한 검사에 한함
	치사성 다발성 익상편 증후군 (Multiple pterygium syndrome, lethal type)
	린치 증후군 (Lynch syndrome)
	에스코바 증후군 (Escobar syndrome)
	초장쇄 acyl-CoA 탈수소효소 결핍증
	카우덴 증후군 (Cowden syndrome 1)
	횡문근양 종양 소인 증후군 (Rhabdoid tumor predisposition syndrome 1)
	포이츠제거스 증후군 (Peutz-Jeghers syndrome)
	HLRCC 신장암 (Hereditary leiomyomatosis and renal cell cancer)

Major Hereditary Gynecologic Cancer Syndromes (HGCS)

Syndrome	Major Gynecologic Malignancies
Hereditary Breast and Ovarian Cancer (HBOC)	Ovarian / Fallopian tube / Peritoneal cancer
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In Vitro Maturation (IVM)

IVM



Why IVM?

- **Minimal or no ovarian stimulation**
- Less dependent on menstrual cycle timing
- May avoid delays in urgent cancer treatment
- Can complement OTC

Current Evidence

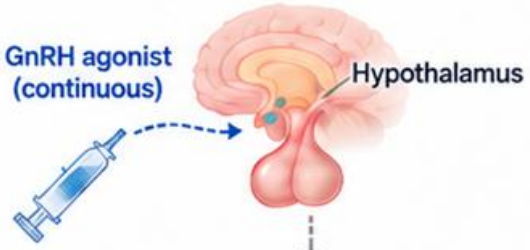
- Overall maturation rate: ~60%
- OTC-derived oocyte maturation: 33.8%
- Clinical evidence in cancer patients: limited
- Long-term safety and live birth data: limited

IVM is promising when conventional COS is not feasible, but remains an emerging technique.

GnRH Agonist for Ovarian Protection

Concept & Mechanism

GnRH agonist administration (during chemotherapy)
↓
Continuous GnRH receptor stimulation
↓
Downregulation of pituitary GnRH receptors (Hypogonadotropic state)
↓
↓ LH / ↓ FSH
↓
Reduced follicular recruitment and activity
↓
Decreased ovarian exposure to chemotoxic damage



- Fewer growing follicles
- Lower ovarian metabolic activity
- Reduced susceptibility to chemotherapy-induced injury

Clinical Evidence (in BC)

PROMISE-GIM6, Lambertini M, et al. J Natl Cancer Inst. 2022

Outcome	CTx. + GnRH-a	CTx. Alone
Early menopause	**8.9%**	25.9%
Menstruation recovery	**72.6%**	64.0%
Long-term DFS / OS	No significant difference	

Limitations

- Breast cancer: Strongest evidence
- Gynecologic cancer data: Limited
- Fertility and pregnancy benefits remain uncertain across cancer types
- **Not a substitute for established FP methods**

GnRH-a may preserve ovarian function during chemotherapy, but is an adjunct-not a substitute for FP.

Surgical Fertility Preservation Before Pelvic RT

Pelvic RT → OV Damage

- Dose-dependent follicular loss
- **~2 Gy:** ~50% reduction in follicular density
- **>5 Gy:** Increased risk of amenorrhea, particularly in older women



Ovarian Transposition

- Relocates ovaries outside the radiation field
- Reduces ovarian radiation exposure
- Established procedure in cervical cancer
- **Ovarian function preserved in ~61% after EBRT**



Uterine Translocation

- Temporarily relocates the uterus outside the radiation field
- Aims to preserve future pregnancy potential
- Limited clinical experience
- **Investigational technique**



Ovarian transposition is clinically established; uterine translocation remains investigational.

Summary & Future Perspectives

Established FP

- Embryo cryopreservation
- Oocyte cryopreservation
- Ovarian tissue cryopreservation (OTC)

Advances in cryopreservation technology

Emerging FP

- In Vitro Maturation (IVM / CAPA-IVM)
- 3D follicle culture
- Artificial ovary

Promising, but not yet established for routine FP

Future Challenges

- Long-term safety and outcomes of OTC
- Gonadotoxicity of targeted & immune therapies
- Better biomarkers of reserve and oocyte quality

Safer, more effective FP strategies

Fertility preservation must evolve together with advances in cancer treatment and hereditary cancer care.

Take-Home Messages

1	**Identify early**	Recognize hereditary cancer risk.
2	**Counsel early**	Before cancer treatment or RRS.
3	**Individualize FP**	Consider age, genetic risk, and reproductive goals.
4	**Consider PGT-M**	For eligible patients with known familial variants.
5	**Use multidisciplinary care**	Oncology · Reproductive Medicine · Genetics

경청해 주셔서 감사합니다

