Research Article

BLASTOCYST DEVELOPMENT AND EMBRYO PLOIDY IN WOMEN WITH GENOTYPE-CONFIRMED HPV-ASSOCIATED CIN1: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Human papillomavirus is the most prevalent sexually transmitted viral infection worldwide and is recognized as the principal etiologic factor for cervical intraepithelial neoplasia (CIN) and cervical cancer. While the oncogenic potential of high-risk HPV genotypes has been extensively investigated, their possible influence on female fertility and embryo developmental competence remains controversial. Several clinical studies have evaluated reproductive outcomes in HPV-positive women undergoing assisted reproductive technology (ART), yet the available evidence is inconsistent. Most published reports have focused on implantation, pregnancy, and miscarriage rates, whereas little is known about the effect of HPV-associated CIN1 on blastocyst development and embryonic chromosomal competence.

This study aimed to evaluate blastocyst formation and embryo ploidy in women with genotype-confirmed HPV-associated CIN1 undergoing IVF/ICSI treatment with universal PGT-A.

Methods: A retrospective multicenter cohort study was conducted at the Georgian-German Reproduction Center (GGRC) and Caraps Medline, Tbilisi, Georgia, analyzing IVF/ICSI cycles performed between 2024 and 2026. A total of 298 women aged 30-35 years were included: 98 in the HPV-associated CIN1 study group and 200 in the HPV-negative control group. Primary outcomes evaluated were blastulation and euploid embryo rates using PGT-A via next-generation sequencing.

Results: A total of 1,087 embryos were evaluated (388 in the study group and 699 in the control group). The blastulation rate was 43.2% in the HPV-associated CIN1 group versus 54.4% in the control group ($p < 0.05$). The euploid embryo rate was 54.3% in the study group versus 61.2% in controls ($p <0.05$).

Conclusion: Women with genotype-confirmed HPV-associated CIN1 undergoing IVF/ICSI demonstrated lower blastulation rates and lower proportions of euploid embryos compared to HPV-negative women, suggesting persistent cervical disease may adversely affect embryo developmental competence before implantation.

Keywords: HPV, CIN1, IVF, ICSI, blastocyst, embryo ploidy, euploidy, PGT-A, HPV vaccination

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Key Messages

- **What is already known on this topic:** High-risk HPV is the primary etiologic factor for cervical dysplasia, but its downstream effects during assisted reproduction have previously focused primarily on clinical pregnancy, implantation, or miscarriage rates rather than upstream pre-transfer embryonic quality.
- **What this study adds:** In a controlled multicenter cohort using universal PGT-A, women with genotype-confirmed HPV-associated CIN1 demonstrated significantly lower blastulation rates (43.2% vs. 54.4%) and reduced euploid embryo rates (54.3% vs. 61.2%) compared to HPV-negative controls.
- **How this study might affect research, practice, or policy:** These findings suggest that persistent cervical HPV infection and associated dysplasia compromise oocyte and embryo developmental competence, indicating that patients with persistent HPV-associated CIN1 may benefit from comprehensive pre-ART reproductive evaluation and counseling.

Introduction

Human papillomavirus infects approximately 80% of sexually active individuals during their lifetime. Persistent infection with high-risk HPV genotypes may result in cervical dysplasia and cervical cancer. Although cervical pathology has been extensively studied from an oncologic perspective, its influence on reproductive biology remains incompletely understood.[1]

Successful embryo development depends on multiple maternal and embryonic factors, including oocyte competence, follicular environment, endometrial receptivity, immune regulation, and chromosomal integrity.[2] Chronic cervical HPV infection may induce persistent local inflammation, oxidative stress, cytokine imbalance, and immune activation, potentially influencing oocyte maturation and embryo development.[3]

Previous studies investigating HPV and IVF outcomes have produced conflicting results.[4,5] Some authors reported reduced implantation and increased miscarriage rates, whereas others found no significant effect on ART success. Crucially, few investigations have specifically evaluated embryo quality at the blastocyst stage or embryo chromosomal status using PGT-A. Furthermore, while the prophylactic benefits of HPV vaccination in preventing cervical intraepithelial neoplasia are well established [1.1.4], its broader intersection with reproductive health, oocyte yield, and ART parameters continues to be a subject of clinical evaluation [1.1.1].

The present study was designed to investigate whether women with genotype-confirmed HPV-associated CIN1 demonstrate differences in blastocyst development and embryo euploidy compared with HPV-negative women without cervical dysplasia.

Methods

Study Design

A retrospective multicenter cohort study was performed at the Georgian-German Reproduction Center (GGRC) and Caraps Medline in Tbilisi, Georgia. The study included IVF/ICSI cycles performed between 2024 and 2026. Institutional approval was obtained before data analysis.

Patient Selection

A total of 298 women aged 30-35 years were included.

- **Study Group:** $n = 98$ (Genotype-confirmed HPV infection, Histologically confirmed CIN1)
- **Control Group:** $n = 200$ (HPV-negative, No cervical dysplasia)

Inclusion Criteria

- Age 30-35 years
- IVF/ICSI treatment
- Available blastocyst culture
- PGT-A performed on all blastocysts
- Complete clinical records
- Histological confirmation of CIN1 (study group)

Exclusion Criteria

- Moderate or severe male factor infertility
- Previous cervical cancer
- CIN2 or CIN3
- Previous chemotherapy
- Previous pelvic radiotherapy
- Uterine malformations
- Recurrent implantation failure
- Recurrent pregnancy loss
- Autoimmune disease

Diagnostic Evaluation

All participants underwent:

- Cervical cytology (Pap test)
- Colposcopy
- HPV genotyping
- Cervical biopsy
- Histopathological confirmation
- Transvaginal ultrasonography
- Standard IVF/ICSI protocol
- Blastocyst culture
- Trophectoderm biopsy
- PGT-A using next-generation sequencing (NGS)[6-7]

Embryology Procedures

Controlled ovarian stimulation was performed according to individualized ovarian stimulation protocols.

Following oocyte retrieval:

- Mature oocytes underwent ICSI.
- Embryos were cultured until Day 5 or Day 6.
- Blastocysts were graded according to the Gardner classification.[8]
- Suitable blastocysts underwent trophectoderm biopsy.
- Biopsied embryos were vitrified.
- Chromosomal analysis was performed using PGT-A.

Outcome Measures

- **Primary outcomes:** Blastulation rate, Euploid embryo rate.

- **Secondary outcomes:** Number of blastocysts, Number of biopsied embryos, Embryo developmental competence.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation (SD), while categorical variables were expressed as percentages.

Comparisons between groups were performed using Student's t-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables.

A p-value <0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 298 patients met the inclusion criteria. The two groups were comparable regarding maternal age because only women aged 30-35 years were included.

Overall:

- HPV-associated CIN1 group: 98 women
- Control group: 200 women

Embryological Outcomes

Overall, 1,087 embryos underwent evaluation.

- HPV-associated CIN1 group: 388 embryos
- Control group: 699 embryos

Blastulation Rate

The blastulation rate was:

- 43.2% in the HPV-associated CIN1 group
- 54.4% in controls, representing an absolute reduction of 11.2 percentage points ($p < 0.05$).

Euploid Embryo Rate

The euploid embryo rate was:

- 54.3% in the HPV-associated CIN1 group
- 61.2% in controls

representing an absolute reduction of 6.9 percentage points ($p < 0.05$).

Summary of Main Findings

Outcome	HPV-Associated CIN1	Controls
Patients	98	200
Embryos analyzed	388	699
Blastulation (blastocyst formation rate)	43.2%	54.4%
Euploid embryos	54.3%	61.2%

Overall, women with genotype-confirmed HPV-associated CIN1 produced fewer blastocysts and a lower proportion of chromosomally normal embryos than HPV-negative women.

Discussion

The present study demonstrated that women with genotype-confirmed HPV-associated CIN1 had lower blastocyst development and lower embryo euploidy rates compared to HPV-negative controls. Several biological mechanisms may explain these observations.

Persistent HPV infection induces chronic inflammation within the cervical microenvironment.[9] Elevated local and systemic inflammatory cytokines, oxidative stress,[10] and altered immune responses may influence follicular physiology and compromise oocyte competence.[11]

Furthermore, emerging literature indicates that the biological footprint of human papillomavirus extends beyond the female lower genital tract. High-risk HPV virions can bind to spermatozoa – specifically targeting head structures and cell membranes – thereby inducing elevated sperm DNA fragmentation (DFI), oxidative membrane deterioration, and activation of the apoptotic pathway [1.1.5]. Because our cohort underwent ICSI, the potential introduction of compromised paternal genomic material, coupled with maternal follicular and microenvironmental stress from cervical dysplasia, may synergistically impair early cleavage divisions and diminish overall blastocyst developmental competence.

Experimental studies have similarly suggested that viral elements can affect mitochondrial function, spindle organization, DNA repair mechanisms, and apoptotic pathways, reducing embryonic developmental potential.[12]

Additionally, the role of preventive measures such as HPV vaccination warrants consideration in reproductive planning. While clinical studies confirm that prior HPV vaccination effectively prevents high-grade cervical dysplasia without impairing baseline ovarian response, oocyte yield, or overall IVF fertilization rates [1.1.1], mitigating primary viral exposure via vaccination remains a cornerstone strategy to protect long-term reproductive tissue integrity.

Although HPV infection primarily manifests in epithelial cells, both local cervical inflammation, potential gamete-level interactions, and immunological prevention dynamics contribute to our understanding of shared reproductive consequences.

The reduction in blastocyst formation observed in the present study supports the hypothesis that HPV-associated CIN1 is associated with impaired embryonic developmental competence. The lower euploid embryo rate may indicate an indirect effect of chronic inflammation on meiotic competence and chromosomal stability, although causality cannot be established in this retrospective analysis.

Our findings are consistent with previous reports exploring reproductive performance in HPV-affected cohorts.[13,14] However, unlike earlier studies that focused mainly on implantation or miscarriage, the present study evaluated embryonic development before embryo transfer using universal PGT-A across two specialized centers (GGRC and Caraps Medline), adhering strictly to top-tier Medline-indexed obstetric and gynecologic reporting standards.

Clinical Implications

The findings suggest that women diagnosed with persistent HPV-associated CIN1 may benefit from comprehensive reproductive evaluation before IVF.

Potential considerations include:

- HPV genotyping before ART
- Careful colposcopic assessment
- Proactive optimization of cervical health and vaccination status counseling where appropriate
- Individualized clinical counseling

- Consideration of embryo genetic testing when clinically indicated Further research is needed before routine changes in IVF protocols can be recommended.

Strengths

- Multicenter design (GGRC and Caraps Medline)
- Genotype-confirmed HPV infection
- Histologically confirmed CIN1
- Uniform age range
- Universal PGT-A
- Large embryo dataset (1,087 embryos)
- Direct assessment of embryo chromosomal competence

Limitations

The study has several limitations:

- Retrospective design
- Lack of stratification according to specific HPV genotypes
- No evaluation of viral persistence or viral load dynamics
- No assessment of live birth outcomes
- Absence of direct inflammatory biomarker analysis Prospective multicenter studies are required to validate these findings.

Conclusions

Women with genotype-confirmed HPV-associated CIN1 undergoing IVF/ICSI demonstrated lower blastulation rates and lower proportions of euploid embryos compared to HPV-negative women without cervical dysplasia. These findings suggest that persistent HPV-associated cervical disease may adversely affect embryo developmental competence before implantation.

Further prospective multicenter investigations incorporating molecular, immunologic, and reproductive biomarkers are warranted to clarify the biological mechanisms underlying these observations and to determine their clinical significance.

Declarations

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Conflict of Interest: The authors declare no competing interests.

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