Cervical Pathology and Connections to Clinical and Health Factors

Ph.D. Thesis Booklet

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5.1 Overview of the Topic

5.1.1 What is the Topic?

The topic is cervical diseases, with a focus on factors influencing cervical dysplasia and cervical cancer, and their roles in disease progression.

5.1.2 What Problem Needs to Be Solved?

The key issue is the high prevalence of cervical cancer and the low rates of vaccination and screening among girls and women. The World Health Organization (WHO) aims to eliminate cervical cancer by 2030, targeting 90% vaccination of girls under 15, 70% screening of women by age 35 with rescreening at 45, and ensuring 90% of women with cervical disease receive treatment.

5.1.3 Why is the Topic Important?

Cervical cancer is the fourth most common cancer in women and a leading cause of cancer-related deaths, particularly in developing countries. It can be effectively prevented and treated through HPV vaccination, screening with Pap smears and HPV tests, and advanced treatments like immunotherapy and targeted therapies.

Despite these advancements, cervical cancer remains prevalent in low-resource settings.

5.1.4 What is the Impact of Our Research?

Our research on factors influencing cervical diseases could improve patient care and aid in personalizing therapies. Identifying new risk factors may enhance public health policies and awareness efforts. Additionally, our findings could support the development of conservative treatments for cervical precancers, particularly for women of childbearing age.

2. OBJECTIVES

2.1. Trichomonas vaginalis- cervical carcinogenesis

With reference to the available literature, this study set out to conduct a comprehensive investigation into the association between TV and HPV, cervical dysplasia, and carcinogenesis. Our hypothesis was that TV presented a risk factor for developing cervical cancer.

2.2. Imiquimod cervical precancer

With reference to the available literature, the aim of this study was to determine the efficacy and safety of topical Imiquimod therapy in reducing the incidence of cervical

intraepithelial neoplasia (CIN) and its impact on HPV clearance.

3. METHODS

This systematic review and meta-analysis adhered to PRISMA 2020 and MOOSE guidelines (see Tables S1-S2) and followed recommendations from the Cochrane Handbook. The pre-study protocol was registered on PROSPERO (Study I: CRD42021286097, Study II: CRD420222870).

3.1 Literature Search and Eligibility Criteria

A systematic search was conducted in five major databases on October 20, 2021 (Study I) and October 10, 2022 (Study II): MEDLINE (via PubMed), Embase, Cochrane CENTRAL, Scopus, and Web of Science. Only peer-reviewed articles were included; no searches were performed on ClinicalTrials.gov, as a preliminary search identified no suitable studies. No filters or restrictions were applied.

3.1.1 Trichomonas Vaginalis

Two PEO frameworks were used to define eligibility. Studies of sexually active (P1) or HPV-positive women (P2) screened for TV infection (E) were included if they reported outcomes such as HPV positivity, cervical dysplasia, or cervical cancer (O1 for P1 and O2 for P2). The control group consisted of TV-negative women. TV detection methods included cytology, wet mount, culture, or PCR, while HPV exposure required nuclear amplification. Studies that diagnosed TV based on clinical features or used HPV cytology alone were excluded due to low sensitivity. For dysplasia outcomes, the Bethesda classification was required for cytological samples, and CIN diagnoses were grouped as LSIL (CIN1) or HSIL (CIN2-3). Eligible study designs included observational studies (cross-sectional, case-control, cohort). Abstracts were excluded, and non-English articles were translated for evaluation.

3.1.2 Imiquimod

Two frameworks were used: CoCoPop for studies without comparators and PICO for studies with comparators. The CoCoPop framework included women with cervical intraepithelial neoplasia (Population) treated with topical Imiquimod (Context), with outcomes (Condition)

including dysplasia regression, treatment success, HPV clearance, and adverse events. The PICO framework assessed women with cervical dysplasia or HPV (P) treated with Imiquimod (I) compared to standard treatments (C). Outcomes (O) included dysplasia regression, HPV clearance, and adverse events. Eligible study designs included cohorts, case-control studies, and randomized controlled trials (RCTs). Follow-up was required, and non-English articles were translated for evaluation.

3.2 Study Selection and Data Collection

Articles were managed using Endnote X9. After removing duplicates, two independent reviewers (BH, EH) conducted title, abstract, and full-text screening, with disagreements resolved by a third reviewer (ZSH). Data were extracted into predefined Excel spreadsheets by two independent reviewers. For Study I, extracted variables included author, publication year, DOI, study design, demography, country, centers, and detection methods. For Study II, variables included author, publication year, DOI, study design, country, study period, centers, follow-up duration, and patient characteristics. Data on outcomes were collected in two-by-two tables, with adjusted odds ratios (ORs) and risk ratios (RRs) extracted where

possible. Disagreements were resolved by consensus with a third reviewer.

3.3 Risk of Bias and Quality Assessment

Study I outcomes were assessed using the Quality in Prognostic Studies (QUIPS) tool, evaluating six domains: study participation, attrition, prognostic factor measurement, outcome measurement, confounding, and statistical analysis reporting. Each domain was classified as low, moderate, or high risk of bias. For Study II, RCTs were evaluated with the Risk of Bias II (ROB II) tool, and non-randomized studies with the ROBINS-I tool. Response rates lacking control groups were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists. The level of evidence was graded using the GRADE approach, with the GradePro tool used for Summary of Findings Tables. Disagreements were resolved by a third reviewer.

3.4 Synthesis Methods

Data synthesis included qualitative and quantitative analyses using R (versions 4.2 and 4.3). A minimum of three studies was required for quantitative analysis, with

results presented in forest plots. Study I subgroup analyses were based on TV detection methods and country of origin, while Study II subgroups were based on article type and cervical dysplasia grade. Pooled ORs and RRs with 95% confidence intervals (CIs) were estimated using random-effects models, and significance was determined at $p < 0.05$. Heterogeneity was assessed using Higgins & Thompson's I^2 and Cochran Q tests, with τ^2 indicating variance in Study II. Fixed-effects models were used for Study II subgroups, with the Cochrane Q test assessing subgroup differences. Publication bias in Study I was assessed using funnel plots and Egger's test, but not in Study II due to limited studies.

4. RESULTS

4.1. Trichomonas vaginalis-cervical carcinogenesis Study I.

4.1.1. The association between TV and HPV infections

Twenty-four studies, representing 7,291 women in the TV infected group and 452,161 in the control group, reported an association between TV and HPV infections. Based on our results, TV-positive women were shown to be 1.79 times more likely to receive a HPV co-infection diagnosis (CI: 1.27–2.53; I^2: 95%) than TV-negative women.

4.1.2. The association between TV and cervical dysplasia

4.1.2.1. HSIL

Regarding the association between TV infection and HSIL, eleven studies reported on 1,796 women in the exposure group and 80,276 women in the control group. TV- infected women were 2.34 times more likely to receive an HSIL diagnosis (CI: 1.10–4.95; I^2: 75%) compared to non-TV-infected women.

4.2.3. The association between TV and cervical cancer

Three articles were subjected to quantitative analysis, with 219 women in the TV positive group and 397 women in the control group. TV-positive women were 5.24 times more likely to have cervical cancer (OR: 5.23; CI: 3.03–9.04; I^2: 3%) than TV-negative women.

4.2. Imiquimod cervical precancer

4.2.1. CIN 2-3 regression

Altogether, 294 women were treated with topical Imiquimod for CIN 2-3. A regression rate of 61% (CI:

0.46–0.75; I^2: 77%) to CIN 1 or no disease was observed following topical Imiquimod therapy

For the experimental group, 196 women were treated with Imiquimod, with 196 women in the control group treated with conization. For women in the conization group, there was a 38% decrease in the risk for persistence or progression in CIN in comparison to women who had received Imiquimod (RR: 0.62; CI: 0.42–0.92; I^2: 64%)

4.2.2. Imiquimod on HPV clearance

Out of the 254 women treated with Imiquimod, 50% (CI: 0.35–0.64; I^2: 64) experienced HPV clearance. A subgroup analysis was conducted, based on the grade of cervical dysplasia. For diagnosed CIN 2-3, there was a HPV clearance rate of 42% (CI: 0.29–0.56; I^2:49%); for diagnosed CIN 1-3, there was a HPV clearance rate of 68% (CI: 0.48–0.84). Finally, for HPV positivity with no CIN, there was a HPV clearance rate of 65% (CI: 0.44–0.83). It must be noted however, that only one study was available for each outcome.

The Imiquimod group comprised 196 women, and the control arm comprised 180 women. HPV clearance as a result of Imiquimod treatment was not better than that

observed in the control group (RR: 1.29; CI: 0.52–3.21; I^2: 80%).

4.2.3 Adverse events

For five studies, it was possible to quantitatively synthesize the adverse events in patients treated with Imiquimod, due to the similar grading system employed by these studies. Side effects were graded on a scale ranging from one to five, with grades defined as mild, moderate, serious, life-threatening, and death.

The most frequent systemic side effects were flu-like symptoms and myalgia; regarding local side effects, the most common was vaginal pruritus .

5. CONCLUSIONS

Our results show that TV infection may increase the odds of cervical lesions and cancer development in sexually active women. In cases of TV diagnosis, clinicians should evaluate HPV and cervical dysplasia.

Our findings show Imiquimod to be safe and effective in reducing CIN and facilitating HPV clearance. In conclusion, while Imiquimod is not a substitute for cone biopsy, it can be a valuable option for the treatment of

high-grade cervical dysplasia. Additionally, Imiquimod could also be considered for the management of low-grade cervical dysplasia.

6. BIBLIOGRAPHY

16.1. Publications related to the thesis

Q1

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Q1

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