Clinical Regression of High-Grade Cervical Intraepithelial Neoplasia Is Associated With Absence of FAM19A4/miR124-2 DNA Methylation (CONCERVE Study)

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PURPOSE Cervical screening can prevent cancer by detection and treatment of cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3). Screening also results in considerable overtreatment because many CIN2/3 lesions show spontaneous regression when left untreated. In this multicenter longitudinal cohort study of women with untreated CIN2/3, the prognostic value of FAM19A4/miR124-2 methylation was evaluated for clinical regression.

PATIENTS AND METHODS Women with CIN2/3 were prospectively followed for 24 months. Surgical excision was replaced by a wait-and-see policy. FAM19A4/miR124-2 methylation was evaluated on all clinician-collected samples and self-collected samples collected at baseline. Every 6 months, human papillomavirus (HPV) testing and cytology were conducted on a clinician-collected sample, and a colposcopic examination was performed by a gynecologist to exclude progression. At the final study visit, two biopsies were taken. Clinical regression was defined as histologically confirmed absence of CIN2+ or an HPV-negative clinician-collected sample with normal cytology. Regression incidences were estimated using the Kaplan-Meier method.

RESULTS One hundred fourteen women (median age, 30 years; range, 20-53 years) were included, 80 of whom were diagnosed with CIN2 and 34 with CIN3. During the study, 65.8% of women (75/114) did not receive surgical treatment. Women with a negative FAM19A4/miR124-2 result on the baseline clinician-collected sample showed more clinical regression (74.7%) than women with a positive methylation result (51.4%, P = .013). Regression in women with a negative FAM19A4/miR124-2 methylation test was highest when cytology was atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesion (88.4%) or HPV16 was negative (85.1%).

CONCLUSION Most women with untreated CIN2/3 and a negative baseline FAM19A4/miR124-2 methylation test showed clinical regression. Methylation, in combination with cytology or HPV genotyping, can be used to support a wait-and-see policy in women with CIN2/3.

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INTRODUCTION Cervical cancer and its precursor lesion cervical intraepithelial neoplasia (CIN) are caused by a persistent high-risk human papillomavirus (HPV) infection.1 HPV vaccination protects against new HPV infections, but cervical screening remains an important secondary prevention method in the coming decades.2 Since treatment of CIN lesions is associated with cervical morbidity and preterm birth3-7 and only a subset of CIN grade 2 (CIN2) and grade 3 (CIN3) will progress to cervical cancer when left untreated8-9 the level of overtreatment should be kept as low as possible. A test that can predict clinical regression of CIN2/3 lesions may help to prevent overtreatment and is urgently needed. Current histopathologic grading of CIN by pathologists cannot discriminate between regressive and non-regressive CIN2 and CIN3. Several biomarkers have been evaluated for their prognostic value such as HPV viral load and immunohistochemical staining of p16INK4A and Ki-67,10 but none of these were able to predict regression or progression of CIN. Recent studies have shown that DNA methylation levels of host cell genes and viral genes increase with severity of CIN grade and are very high in cervical cancer.11-15 The QIAseq FAM19A4/miR124-2 DNA methylation test (Qiagen, Hilden, Germany) is a quantitative methylation-specific polymerase chain reaction that can detect small amounts of methylated DNA and...
provides high sample throughput. The FAM19A4/miR124-2 methylation test has shown to detect nearly all cervical cancers and all CIN lesions associated with a long-lasting HPV infection. The FAM19A4/miR124-2 methylation test was evaluated in a large multicenter cohort, resulting in a sensitivity of 77.2% and specificity of 78.3% for CIN3, and 95.0% sensitivity for cervical cancer. The long-term negative predictive value showed a similar reassurance against CIN3 and cervical cancer compared with cytology after 14 years of follow-up. On the basis of these results, we assume that FAM19A4/miR124-2 methylation detects CIN2/3 lesions at highest risk of progression to cervical cancer.

Here, we present the results of the CONCERVE study, which is a multicenter longitudinal cohort study, where standard surgical excision of CIN2/3 lesions is replaced by a wait-and-see policy for a period of 24 months. The aim of this study is to evaluate the prognostic value of FAM19A4/miR124-2 methylation for clinical regression in women with untreated CIN2 or CIN3.

PATIENTS AND METHODS

Study Population and Sample Collection

The study Protocol (online only) of the CONCERVE study has been published before and is shown in Figure 1. The three participating clinics were OLVG (Amsterdam), Flevoziekenhuis (Almere), and Bergman Clinics (Amsterdam). Women referred for colposcopy and diagnosed with biopsy-confirmed CIN2 or CIN3 were asked to participate.

Women age 18-55 years were eligible for participation in the study if the colposcopic volume of the CIN2 or CIN3 lesion was < 50% of the visible cervix. Exclusion criteria included pregnancy at the time of inclusion, history of cervical pathology (ie, CIN1 or worse) in the preceding 2 years, adenocarcinoma in situ (AIS), transformation zone not fully visible at colposcopy, prenatal diethylstilbestrol exposure, concomitant cancer, and insufficient Dutch or English language skills. After inclusion, participants were sent a self-sampling device (Evalyn brush; Rovers Medical Devices BV, Oss, the Netherlands) for self-collection of cervicovaginal material (referred to as baseline self-collected sample). Clinician-collected cervical samples that initiated referral for colposcopy were requested for further analysis (referred to as baseline clinician-collected sample). HPV testing and methylation analysis were performed on both baseline self-collected and clinician-collected samples. All clinical samples were stored in ThinPrep PreservCyt Solution. HPV testing and cytology were performed on all clinician-collected samples. Cytology was classified according to the CISOE-A classification and translated into the Bethesda classification. If cytology showed no abnormalities at the 12-month or 18-month study visit, colposcopic examination could be omitted. Cervical biopsies were taken by the gynecologist on the basis of the colposcopic impression. If the transformation zone was not completely visible at colposcopy, women were excluded from...
Clinical progression was an indication for surgical treatment and was defined as an increase in colposcopic volume of the lesion covering more than 50% of the visible cervix, histologic progression from CIN2 to CIN3 or from CIN3 to cervical cancer, and/or histologic diagnosis of AIS. At the final study visit at 24 months, two colposcopy-directed biopsies were taken, or two random biopsies were taken if there was no visible lesion. Participants with a CIN2 or worse at the final study visit were recommended surgical treatment according to national guidelines. All participants provided written informed consent. The study was approved by the Medical Ethics Committee of Amsterdam UMC, VU University Medical Center (2016/471), and
registered as NTR6069/NL5794 in the Netherlands National Trial Registry. Additional ethical approval was obtained from the participating clinics. This study followed the REMARK guidelines.

**HPV Testing and DNA Methylation Analysis**

Molecular testing was performed blinded for cytology and histology outcomes at the Department of Pathology of Amsterdam UMC. The QIAscreen HPV PCR Test (Qiagen) was used for high-risk HPV testing with separate genotyping for HPV16, HPV18, and a pool of 13 other high-risk HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 67, and 68). The QIAscreen Methylation Test (Qiagen) was used for FAM19A4/miR124-2 methylation testing on bisulfite-converted DNA. The methylation test result was labeled positive if the QIAscreen Methylation Test result exceeded the preset threshold for methylation positivity. Baseline clinician-collected samples stored in SurePath (n = 11) were not tested for FAM19A4/miR124-2 methylation because of insufficient DNA quality after DNA isolation.

**Sample Size Calculation**

We assumed that the regression probability was 15% for methylation-positive and 45% for methylation-negative women, and that 50% of the women were methylation-positive. Then, a sample size of 100 provides a power of 87% to detect a difference in regression probability (significance level .05, two-sided) and a 95% CI with width below 20%.

**Statistical Analysis**

The primary study end point was clinical regression. We defined clinical regression as histologically confirmed absence of CIN2+ or an HPV-negative clinician-collected sample with normal cytology in case histology was absent, and no histologic diagnosis of CIN2+ during further follow-up. We estimated the cumulative incidence of clinical regression by the Kaplan-Meier method where time to event was defined as the number of months between baseline histology and the date of clinical regression. We assumed that the probability of clinical regression was very low after an indication for surgical treatment in which case time to event was censored at the end of the study. If neither clinical regression nor surgical treatment indication was reported, time to event was censored at the date of the last study visit. The maximum follow-up time was 30 months instead of 24 months because of COVID-19–related delays for nine women, but cumulative incidences should be interpreted as 2-year incidences. Separate Kaplan-Meier curves were estimated for strata defined by screening age (ie, < 29 years v ≥ 29 years), smoking, oral contraceptive use, colposcopic volume, methylation, cytology (ie, atypical squamous cells of undetermined significance [ASC-US] and low-grade squamous intraepithelial lesion [LSIL] v high-grade squamous intraepithelial lesion [HSIL]), and HPV16 and HPV16/18 genotyping. Samples were considered HPV16-positive if HPV16 was present as a single infection or as a multiple infection together with at least one other HPV type. Samples were considered HPV16/18-positive if HPV16 and/or HPV18 was present. Kaplan-Meier curves were also estimated for combined strategies with colposcopic volume, methylation, cytology, and/or HPV16 genotyping. Kaplan-Meier curves were compared using the log-rank test and 95% CIs were estimated using Greenwood’s formula. To study the effect of follow-up biopsies on the regression incidences, we repeated the main analyses with time censored at the moment a biopsy was taken during follow-up. Cases with missing or invalid values were omitted from the analysis. Two-sided P values below .05 were considered significant. Statistical analyses were performed in SPSS Statistics (version 26; IBM Corp, Armonk, NY) and GraphPad Prism (version 9; GraphPad Software, San Diego, CA).

**RESULTS**

From May 2017 to January 2018, 114 women were included, 80 of whom were diagnosed with CIN2 and 34 with CIN3. Baseline characteristics are shown in Table 1. The median age at inclusion was 30 years (range, 20-53 years). Median time between baseline clinician-collected sample and baseline histology was 28 days. Clinical regression occurred in 67 women and clinical progression in 25 women. Of the progression cases, 20 were attributable to histologic progression from CIN2 to CIN3, four to an increase in colposcopic volume > 50%, and one to a histologic diagnosis of AIS. None of the women were diagnosed with cervical cancer. In total, 39 women received surgical treatment because of clinical progression (n = 24), a persistent CIN2 or CIN3 lesion at the final study visit (n = 8), or at their own request (n = 7). Three women denied surgical treatment: one woman with histologic progression from CIN2 to CIN3 and two women with a persistent CIN2/3 at the final study visit. Altogether, in 65.8% (75/114) of women, no surgical excision was performed.

Women without follow-up visits after baseline (n = 2) were excluded from the clinical regression analysis. Lesions with a colposcopic volume of < 25% showed more regression (78.5%; 95% CI, 72.3 to 83.5) than lesions with a colposcopic volume of 25%-50% (35.5%; 10.9 to 61.7; P < .001; Appendix Fig A1, online only). Clinical regression was not significantly associated with age, smoking, oral contraceptive use, and baseline cytology (P = .146 to .579, Appendix Fig A1).

Baseline clinician-collected and self-collected samples for methylation and HPV testing were available for 106 and 109 women, respectively. The results, overall and stratified by baseline histology, are presented in Table 2. CIN2/3 in women with a methylation-negative baseline clinician-collected sample showed more regression after 2 years of follow-up (74.7%; 65.7 to 81.7) than CIN2/3 in women...
with a methylation-positive baseline clinician-collected sample (51.4%; 34.6 to 65.9; \( P = .013 \); Fig 2). Similar findings were found for CIN2/3 in women with a methylation-negative baseline self-collected sample (73.4%; 65.5 to 79.8) compared with CIN2/3 in women with a methylation-positive baseline self-collected sample (48.6%; 28.8 to 65.9; \( P = .020 \); Appendix Fig A1). Similarly, in women with an HPV-positive baseline clinician-collected sample, CIN2 showed more regression when HPV16 was not present (74.5%; 65.4 to 81.5) than when HPV16 was present (50.8%; 35.3 to 64.4; \( P = .024 \); Appendix Fig A1). Similarly, in women with an HPV-positive baseline self-collected sample, CIN2 showed more regression when HPV16 was not present (76.5%; 67.7 to 83.2) than when HPV16 was present (39.8%; 20.2 to 58.8; \( P < .001 \); Appendix Fig A1). The results were comparable for HPV16 on clinician-collected samples (63.5%; 49.9 to 74.4) than after a methylation-positive baseline clinician-collected sample (35.9%; 15.7 to 56.7; \( P = .032 \). In women with an HPV-positive clinician-collected sample, clinical regression was marginally higher after an HPV16-negative result (63.3%;

### TABLE 1. Baseline Characteristics

| Characteristic       | No. (%) |
|----------------------|---------|
| Age, years           |         |
| 20-24                | 9 (8)   |
| 25-29                | 22 (19) |
| 30-34                | 52 (46) |
| 35+                  | 31 (27) |
| Colposcopic impression |       |
| No dysplasia        | 3 (3)   |
| CIN1                 | 47 (41) |
| CIN2                 | 55 (48) |
| CIN3                 | 8 (7)   |
| Missing              | 1 (1)   |
| Colposcopic volume  |         |
| No lesion            | 4 (4)   |
| < 25%                | 79 (69) |
| 25%-50%              | 27 (24) |
| Missing              | 4 (4)   |
| Smoking              |         |
| Never                | 82 (72) |
| Stopped              | 7 (6)   |
| Yes                  | 24 (21) |
| Missing              | 1 (1)   |
| Hormonal contraception |       |
| Oral                 | 40 (35) |
| Mirena IUD           | 25 (22) |
| NuvaRing             | 4 (4)   |
| None                 | 45 (39) |

Abbreviations: CIN1, cervical intraepithelial neoplasia grade 1; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; IUD, intrauterine device.

### TABLE 2. Baseline Cytology, Methylation, and HPV Genotyping Results Stratified by Baseline Histology Result

| Biomarker Result                   | CIN2 | CIN3 | Total |
|------------------------------------|------|------|-------|
| Cytology<sup>a</sup>               |      |      |       |
| NILM                               | 1    | 0    | 1     |
| ASC-US/LSIL                        | 46   | 13   | 59    |
| HSIL                               | 32   | 20   | 52    |
| Methylation<sup>a,b</sup>          |      |      |       |
| Positive                           | 25   | 19   | 44    |
| Negative                           | 44   | 5    | 49    |
| Invalid                            | 0    | 2    | 2     |
| Methylation on self-collected samples |    |      |       |
| Positive                           | 19   | 13   | 32    |
| Negative                           | 57   | 17   | 74    |
| Invalid                            | 2    | 1    | 3     |
| HPV genotyping<sup>c</sup>         |      |      |       |
| HPV-positive                       | 73   | 30   | 103   |
| HPV16<sup>c</sup>                  | 32   | 22   | 54    |
| HPV18<sup>c</sup>                  | 14   | 4    | 18    |
| HPV other<sup>c</sup>              | 53   | 17   | 70    |
| HPV-negative                       | 1    | 0    | 1     |
| Invalid                            | 2    | 0    | 2     |
| HPV genotyping on self-collected samples |      |      |       |
| HPV-positive                       | 66   | 22   | 88    |
| HPV16<sup>c</sup>                  | 24   | 17   | 41    |
| HPV18<sup>c</sup>                  | 11   | 3    | 14    |
| HPV other<sup>c</sup>              | 46   | 11   | 57    |
| HPV-negative                       | 12   | 9    | 21    |
| Invalid                            | 0    | 0    | 0     |

Abbreviations: ASC-US/LSIL, atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesions; NILM, negative for intraepithelial lesion malignancy.

<sup>a</sup>On clinician-collected samples.
<br><sup>b</sup>Samples stored in SurePath (n = 11) were not tested with the QIAsure methylation test because of insufficient DNA quality after DNA isolation.
<br><sup>c</sup>Samples with multiple infections were calculated separately for HPV16, HPV18, and HPV other.

Censoring at the time of a follow-up biopsy led to slightly lower clinical regression incidences, but differences between strata remained (Appendix Fig A2, online only). Clinical regression was higher after a methylation-negative baseline clinician-collected sample (63.5%; 49.9 to 74.4) than after a methylation-positive baseline clinician-collected sample (35.9%; 15.7 to 56.7; \( P = .032 \). In women with an HPV-positive clinician-collected sample, clinical regression was marginally higher after an HPV16-negative result (63.3%;
The combined effect of methylation on baseline clinician-collected samples and colposcopic volume is presented in Figure 3A. For lesions with a colposcopic volume < 25%, clinical regression incidence was 81.0% (71.8 to 87.7) when the clinician-collected sample was methylation-negative and 72.6% (58.8 to 82.7) when the clinician-collected sample was methylation-positive ($P = .423$). For lesions with a colposcopic volume of 25%-50%, clinical regression was higher after a methylation-negative sample (67.3%; 41.3 to 83.7) than after a methylation-positive sample (16.7%; 0.0 to 77.8; $P = .002$).

The two-way interaction effects of methylation, HPV16 genotyping, and cytology of baseline clinician-collected samples on clinical regression are presented in Figures 3B-3D. In women with ASC-US/LSIL, clinical regression was higher when methylation was negative (88.4%; 81.7 to 92.7) than when methylation was positive (61.8%; 40.6 to 77.3; $P = .006$). However, in HPV-positive women with ASC-US/LSIL, clinical regression was similar after an HPV16-negative result (78.8%; 68.1 to 86.3) and after an HPV16-positive result (64.9%; 45.9 to 78.6; $P = .296$). Conversely, in women with HSIL, clinical regression was not significantly different after a methylation-negative result (53.8%; 32.0 to 71.4) and after a methylation-positive result (39.6%; 15.3 to 63.3; $P = .413$), but was nearly significantly different after an HPV16-negative result (66.3%; 48.0 to 79.4) and after an HPV16-positive result (37.3%; 15.7 to 59.2; $P = .061$).

Combined HPV16 genotyping and methylation testing in women with an HPV-positive baseline clinician-collected sample showed a high clinical regression incidence of 85.1% (77.2 to 90.4) after a double-negative result and a substantially lower incidence of 44.7% (20.8 to 66.2) after a double-positive result. Clinical regression reached an intermediate level of 56.9% (35.3 to 73.7) after an HPV16-positive/methylation-negative result and 61.9% (39.4 to 78.1) after an HPV16-negative/methylation-positive result. Clinical regression incidences in the four categories were significantly different ($P = .018$, Fig 3D).

**DISCUSSION**

This multicenter longitudinal cohort study showed high clinical regression of CIN2 and CIN3 after conservative management. Of the 114 women with CIN2 or CIN3, 75 women (65.8%) did not receive surgical excision after 2 years of follow-up. Clinical regression was significantly associated with methylation and HPV16 genotyping, irrespective of whether the evaluation was done on a clinician-collected or self-collected sample. Clinical regression in methylation-negative women with ASC-US/LSIL or an HPV16-negative result was at least 85%, which seems high enough to support a wait-and-see policy to avoid unnecessary CIN2/3 treatment and prevent obstetric complications. Colposcopic volume could also predict clinical regression, but the

49.0 to 74.6) than after an HPV16-positive result (37.0%; 18.9 to 55.2; $P = .085$).

**FIG 2.** Cumulative regression incidences by Kaplan-Meier analysis stratified by methylation results on baseline clinician-collected samples and self-collected samples. CIN2/3, cervical intraepithelial neoplasia grade 2 or 3; MM, methylation marker.
assessments of colposcopic volume is quite variable since it depends on the subjective interpretation of the gynecologist. There was a marked effect of methylation on regression in women with ASC-US/LSIL, but no effect in women with HSIL, indicating that methylation strengthens the histologic interpretation of CIN2/3 found after minor cytologic abnormalities. The effects of methylation and HPV16 genotyping on clinical regression were complementary, since clinical regression was higher in women with an HPV16-negative and methylation-negative (double-negative) result than in single-negative women. This illustrates that genotyping and methylation are independent factors, where HPV16 is a viral marker related to the oncogenic potential of an infection and methylation is a host cell marker that distinguishes early from advanced lesions on the basis of the level of epigenetic alterations.15

The prognostic value of HPV16 for regression of CIN2/3 has been studied in several other studies.26-28 In general, clinical regression was negatively associated with HPV16 positivity, and this finding was confirmed in this study. The association between clinical regression and HPV16 status reflects the high oncogenic potential of HPV16 being the cause of the majority of cervical cancers.29 A main addition of our study is that with combined HPV16 and methylation

FIG 3. Cumulative regression incidences by Kaplan-Meier analysis: (A) combined colposcopic volume and methylation results on baseline clinician-collected samples; (B) combined methylation and cytology results on baseline clinician-collected samples; (C) combined cytology and HPV16 genotyping results on baseline clinician-collected samples, and (D) combined methylation and HPV16 genotyping results on baseline clinician-collected samples. ASC-US/LSIL, atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions; CIN2/3, cervical intraepithelial neoplasia grade 2 or 3; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesions; MM, methylation marker.
an increase in colposcopy referral rate compared with the cytology-based program, mainly caused by the direct referral of HPV-positive women with ASC-US/LSIL.35-37 A recent post hoc analysis of two Dutch screening trials showed that HPV-positive women with ASC-US/LSIL and a negative methylation test have a CIN3+ risk of only 9.8% compared with a CIN3+ risk of 33.1% in women with ASC-US/LSIL and a positive methylation test.38 Our current study showed that even when CIN2/3 is detected in methylation-negative women with ASC-US/LSIL, the probability of regression is nearly 90%. Together, these results support the implementation of methylation in cervical screening, possibly in combination with HPV16 genotyping, to triage HPV-positive women with ASC-US/LSIL for colposcopy.

In 2017, HPV-based cervical screening with cytology triage was implemented in the Netherlands. This led to a two-fold increase in colposcopy referral rate compared with the cytology-based program, mainly caused by the direct referral of HPV-positive women with ASC-US/LSIL.35-37 A recent post hoc analysis of two Dutch screening trials showed that HPV-positive women with ASC-US/LSIL and a negative methylation test have a CIN3+ risk of only 9.8% compared with a CIN3+ risk of 33.1% in women with ASC-US/LSIL and a positive methylation test.38 Our current study showed that even when CIN2/3 is detected in methylation-negative women with ASC-US/LSIL, the probability of regression is nearly 90%. Together, these results support the implementation of methylation in cervical screening, possibly in combination with HPV16 genotyping, to triage HPV-positive women with ASC-US/LSIL for colposcopy.

Our study differed from other studies evaluating regression in CIN because we included both CIN2 and CIN3 of women age 18-55 years, whereas most other studies restricted to CIN2 in young women. However, the proportion of CIN3 in our study was still lower than that observed in clinical practice. Since in clinical practice a wait-and-see policy will most likely be implemented for small CIN2/3 lesions, we only included lesions with a colposcopic volume < 50% of the visible cervix. Another limitation is that CIN diagnosis was obtained from local pathology laboratories, and misclassification cannot be ruled out because CIN grading is known to be subject to interobserver variability.39 However, our study aimed to reflect clinical practice to gain insight into the real-world impact of a wait-and-see policy. Furthermore, we cannot rule out that the biopsy procedures had a curative effect, especially in lesions with a colposcopic volume < 25%, but the significant difference in clinical regression between methylation-positive and methylation-negative lesions with a colposcopic volume of 25%-50% underlines the prognostic value of DNA methylation. Besides, in the sensitivity analysis, we showed that the effect of censoring data after a follow-up biopsy on the reported regression incidences was limited. We further remark that biopsies as performed in our study are needed for histologic confirmation of a suspected area, which means that the reported regression rates are representative of clinical practice.

This study showed that a negative FAM19A4/miR124-2 methylation test was able to identify women with CIN2/3 who had the highest chance of clinical regression. FAM19A4/miR124-2 methylation on a clinician-collected or self-collected sample can be used to guide a wait-and-see policy in women with CIN2/3. Our study supports a strategy where lesions are immediately treated only when the methylation or HPV16 genotyping result is positive and close surveillance is applied otherwise. A wait-and-policy would be most beneficial for women of reproductive age to prevent the risk of obstetric complications.

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DATA SHARING STATEMENT
Individual participant data will be made available to researchers who provide a methodologically sound proposal for meta-analyses. Additional approval of the institutional review board is needed.

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Methylation Predicts Regression of High-Grade CIN

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Clinical Regression of High-Grade Cervical Intraepithelial Neoplasia Is Associated With Absence of FAM19A4/miR124-2 DNA Methylation (CONCERVE Study)

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FIG A1. Cumulative regression incidences by Kaplan-Meier analysis: (A) cytology results on baseline clinician-collected samples, (B) HPV16 genotyping results on baseline clinician-collected samples, (C) HPV16 genotyping results on baseline self-collected samples, (D) colposcopic volume of the lesion, (E) HPV16/18 genotyping results on baseline clinician-collected samples, (F) HPV16/18 genotyping results on baseline self-collected samples, (G) smoking, (H) screening age, and (I) oral contraceptive use. ASC-US/LSIL, atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesions; OC, oral contraceptives.
FIG A2. Cumulative regression incidences by Kaplan-Meier analysis with time censored at the moment a biopsy was taken during follow-up: (A) methylation results on baseline clinician-collected samples and (B) HPV16 genotyping results on baseline clinician-collected samples. HPV, human papillomavirus; MM, methylation marker.