



Short Communication

Preterm birth rate after bivalent HPV vaccination: Registry-based follow-up of a randomized clinical trial

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ABSTRACT

A registry-based follow-up of pregnancy data until the end of 2014 was conducted based on a community-randomized trial to assess human papillomavirus (HPV) vaccination strategies and a reference cohort from the same community with no intervention. Our objective was to determine whether prophylactic HPV vaccination (three doses of Cervarix® (AS04-HPV-16/18)-vaccine) affects preterm birth (PTB) rates. All identified 80,272 residents in 1992–95 birth cohorts in Finland were eligible for the trial and 20,513 of 39,420 (51.9%) females consented to participate. The final study population consisted of age-aligned 6226 HPV16/18 vaccinated females and 1770 HBV vaccinated (Engerix® B, hepatitis B-virus vaccine) females that did not receive HPV vaccine at the age of 18 from the 1992–93 birth cohorts, and 19,849 females from the 1990–91 non-vaccinated reference birth cohorts. We compared the rates of preterm (22 + 0–36 + 6 pregnancy weeks) and early preterm (22 + 0–31 + 6) per term (at least 37 + 0) singleton births among the HPV- and non-HPV-vaccinated women, using nationwide Medical Birth Registry data. We observed 409 singleton first pregnancies lasting at least 22 + 0 weeks among 6226 HPV-vaccinated and 1923 among 21,619 non-HPV-vaccinated women. In the first pregnancy the PTB rate was 13/409 (3.2%) among the HPV-vaccinated and 98/1923 (5.1%) among the non-HPV-vaccinated (OR 0.61, 95% CI 0.34–1.09). Early preterm birth rate was 0/409 (0%) in the HPV-vaccinated women and 20/1923 (1.0%) in the non-HPV-vaccinated women ($p = 0.04$). PTB rate, especially early PTB rate, was lower among the HPV-vaccinated women. Reduction of PTB incidence after prophylactic HPV vaccination would lead to public health benefits globally. Trial Registration:NCT00534638

1. Introduction

Prophylactic human papillomavirus (HPV) vaccines are safe (Lehtinen et al., 2016) and highly efficacious against HPV-infection and high-grade cervical intraepithelial neoplasia (CIN) (Lehtinen and Dillner, 2013). Evidence on efficacy against invasive HPV-associated cancers has emerged through population-based registry linkages (Lei et al., 2020; Luostarinen et al., 2018).

Young women have the highest prevalence of HPV-infections, most of which are acquired after sexual debut. Frequent screening and local treatment of CIN has been associated with an at least two-fold risk of preterm birth (PTB, delivery before 37 pregnancy weeks) in subsequent pregnancies (Habbema et al., 2017; Kyrgiou et al., 2016), and increased perinatal mortality (Kyrgiou et al., 2016). During cervical conization a part of the cervix, that plays a role in both mechanical support during pregnancy and an immunological barrier against ascending infections, is

Abbreviations: CIN, Cervical intraepithelial neoplasia; HBV, Hepatitis B-virus; HPV, Human papillomavirus; PTB, Preterm birth; SGA, Small for gestational age.

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removed. Furthermore, the presence of CIN alone, without treatment, has been associated with increased risk for PTB (Kyrgiou et al., 2016). PTB itself is a complex phenomenon resulting possibly from multiple simultaneous etiologic pathways relating to both mother and fetus (Villar et al., 2012) and can be either spontaneous or iatrogenic. The presence of intrauterine infection and inflammatory processes as well as cervical insufficiency have both been suggested as causes of spontaneous PTBs (Romero et al., 2006).

A recent report from Australia found that increasing HPV vaccination coverage was associated with a small reduction in small for gestational age (SGA) infants and preterm birth rate ratios (Yuill et al., 2020). In maternal cohorts with 60–80% 3-dose HPV vaccination coverage, the SGA rate ratio was 10% and PTB rate 3% lower compared to non-vaccinated cohorts (Yuill et al., 2020). Here we report the first results on preterm birth incidence after HPV vaccination of adolescent girls in a randomized setting based on national registry follow-up of the GSK-sponsored HPV-040 trial (NCT00534638)(Lehtinen et al., 2016).

2. Methods

In 2007 Finland launched a community-randomized trial to assess safety and effectiveness of HPV vaccination strategies, described in detail in previous publications (Lehtinen et al., 2015; Vanska et al., 2020). The Finnish Population Register Centre was used to identify all 80,272 residents born in 1992–1995 in 33 communities. Altogether 20,513 of 39,420 (51.9%) females consented to participate. The 33 municipalities were randomized into three study arms. Before randomization the arms were stratified by low (<20.5%), moderate (20.5% to 24.0%) and high (>24%) background HPV16/18 seroprevalence to decrease arm-wise heterogeneity (Lehtinen et al., 2015). In

Arms A and B female participants were randomly assigned to receive Cervarix® (AS04-HPV-16/18)-vaccine (90%) or Engerix® B (hepatitis B-virus, HBV)-vaccine (10%). In Arm C communities all were assigned to receive the HBV-vaccine. The second and third doses of the two vaccines (at months 1 and 6) were given to 99% of all participants before age 16 (Fig. 1). Vaccination with the HPV-vaccine was offered at the age of 18.5 years to the participants who had received the HBV-vaccine (Vanska et al., 2020).

The 1992–93 birth cohorts included 20,464 invited girls of whom 10,257 consented to participate in the trial and associated health-registry follow-up and were included in the current study (Lehtinen et al., 2015). Anonymous health-registry linkage was used to identify 19,849 female residents of the same 33 municipalities from the 1990–91 birth cohorts serving as the reference cohort with no known intervention. The 1994 and 1995 birth cohorts of the original community-randomized trial were not included in the current study, because of shorter follow-up time due to their younger age. The vaccination status of the non-vaccinated reference cohort could not be ascertained, but the Finnish national HPV-vaccination program was launched in 2013 starting from the 1998 female birth cohort. Opportunistic HPV-vaccination outside the community-randomized trial involving the 1992–1995 birth cohorts was negligible according to the Finnish Medical Drug Agency.

Data on pregnancies and deliveries were retrieved from the Finnish Medical Birth Registry for women born in 1990–91 from 2006 until the end of 2012 and for women born in 1992–93 from 2008 until the end of 2014 (equivalent of follow-up until the age of 22) (Fig. 1). Numbers of early preterm (pregnancy duration between 22 + 0 to 31 + 6 weeks) and preterm (pregnancy duration between 22 + 0 to 36 + 6 weeks) singleton pregnancies per number of full term (pregnancy duration at least 37 + 0

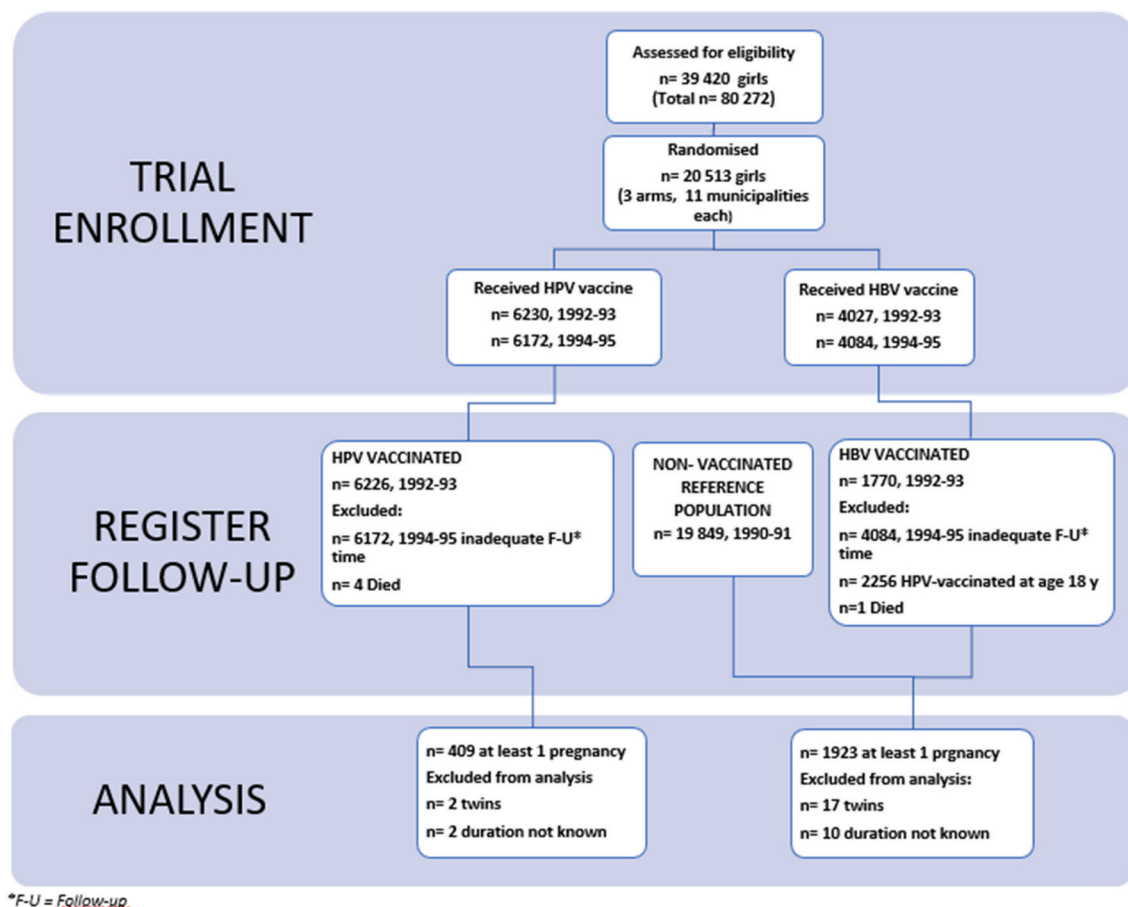


Fig. 1. CONSORT flow diagram.

weeks) singleton pregnancies were compared between the HPV vaccinated, HBV vaccinated, and all non-HPV vaccinated (non-vaccinated reference cohort and HBV vaccinated together). Women cross-vaccinated after HBV vaccine (*n* = 2256) at the age of 18.5 were excluded from all analyses (Fig. 1).

2.1. Statistical analyses

Odds ratios and corresponding 95% confidence intervals using binomial distribution were calculated using *epitab* commands in Stata, release 15 (StataCorp, College Station, Tx, US). In case of zero observations, Fisher’s exact test was used to calculate the corresponding *p*-value. All statistical tests were two-sided.

3. Results

The final study cohort comprised of 6226 HPV-vaccinated and 1770 HBV-vaccinated women and 19,849 similarly aged non-vaccinated reference female residents from the same 33 municipalities. By the age of 22 the number of women with at least one singleton pregnancy lasting 22 weeks or more was 409/6226 (6.6%) in HPV-vaccinated, 180/1770 (10.2%) in HBV-vaccinated, and 1746/19,879 (8.8%) in non-vaccinated reference cohort.

The overall PTB rates (delivery before 37 pregnancy weeks) were 16/481 (3.3%), 13/227 (5.2%), and 100/2157 (4.6%) among the HPV vaccinated, HBV vaccinated, and non-vaccinated, respectively (Table 1). In the first pregnancy alone the overall PTB rate (delivery before 37 weeks) was 13/409 (3.2%) among the HPV-vaccinated and 98/1923 (5.1%) among the non-HPV-vaccinated (OR 0.61, 95% CI 0.34–1.09). Among the HBV-vaccinated the overall PTB rate in the first pregnancy was 10/180 (5.6%), (OR 0.56, 95% CI 0.24–1.27, compared to the HPV-vaccinated). (Table 1).

The early PTB rate (pregnancy duration between 22 + 0 to 31 + 6) in the first pregnancy was 0/409 (0%) in the HPV-vaccinated group and 20/1923 (1.0%) in the non-HPV-vaccinated group (OR 0, 95% CI 0–0.89, *p* = 0.04) and the PTB rate (pregnancy duration between 32 + 0 to 36 + 6) in the first pregnancy 13/409 (3.2%) in the HPV-vaccinated group and 78/1923 (4.1%) in the non-HPV-vaccinated group (OR 0.78, 95% CI 0.43–1.40) (Table 1).

4. Discussion

4.1. Main findings

Overall preterm birth rate in the first pregnancy and across all pregnancies was lower among the previously HPV vaccinated compared to women of similar age who had not received the HPV vaccine, although the finding did not have nominal statistical significance. The reduction in PTB incidence was most pronounced and reached statistical significance in early preterm pregnancies lasting less than 32 pregnancy weeks where the PTB-related morbidity and mortality are highest.

4.2. Strengths and limitations

The follow-up pregnancy incidence and duration was based on nationwide registries with excellent coverage and quality (Gissler et al., 1995). Due to the follow-up lasting only until the age of 22, the results are based on small numbers, which might both predispose to spurious statistically significant associations as well as to low statistical power to detect true positive associations with nominal statistical significance. Exclusion of 2256 of the 4026 HBV vaccinated females who received the HPV-vaccine at the age of 18.5 years was done to reduce the potential residual confounding. Our results are in line with previous findings from a different setting (Yuill et al., 2020) and can therefore be considered to represent the latter scenario of type II error, and additional studies with more extensive datasets are naturally warranted. These findings,

Table 1 Duration and number of pregnancies among HPV-vaccinated and hepatitis B vaccinated and non-vaccinated reference cohort.

| Vaccination status | HPV ^a | | | | | HBV ^{b,c} | | | | | HBV ^{b,c} or unvaccinated | | | | | | | | | |
|--------------------------------|--------------------|-----------|----------|----------|------------|--------------------|-----------|----------|----------|------------|------------------------------------|------------|-----------|----------|-------------|-------------|------------|-----------|----------|-------------|
| | Order of pregnancy | | | | | Total | | | | | Total | | | | | Total | | | | |
| | 1st | 2nd | 3rd | 4th | Total | 1st | 2nd | 3rd | 4th | Total | 1st | 2nd | 3rd | 4th | Total | 1st | 2nd | 3rd | 4th | Total |
| Duration of pregnancy (weeks) | | | | | | | | | | | | | | | | | | | | |
| Early preterm 22 + 0 to 31 + 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 1 | 1 | 0 | 22 | 20 | 1 | 1 | 0 | 22 |
| Preterm 32 + 0 to 36 + 6 | 13 | 3 | 0 | 0 | 16 | 10 | 3 | 0 | 0 | 13 | 68 | 9 | 1 | 0 | 78 | 78 | 12 | 1 | 0 | 91 |
| Term ≥ 37 + 0 | 396 | 68 | 1 | 0 | 465 | 170 | 41 | 2 | 1 | 214 | 1658 | 361 | 36 | 2 | 2057 | 1825 | 405 | 38 | 3 | 2271 |
| Total | 409 | 71 | 1 | 0 | 481 | 180 | 44 | 2 | 1 | 227 | 1746 | 371 | 38 | 2 | 2157 | 1923 | 418 | 40 | 3 | 2384 |

^a CervarixVR (AS04-HPV-16/18) -vaccine.

^b EngerixIM B (hepatitis B-virus, HBV) -vaccine.

^c Women cross-vaccinated with HPV-vaccine at the age of 18.5 (*n* = 2256) excluded.

however, may well be important, as globally annually close to 15 million babies, approximately 11% of all births, are born preterm and close to 1 million babies die due to related complications (Blencowe et al., 2012).

We also observed a lower rate of at least one singleton pregnancy lasting over 22 weeks among the HPV-vaccinated. The randomization did not account for possible differences in fertility rates between municipalities or age groups, as the primary objective of the original study was to assess the effectiveness of HPV vaccination on HPV prevalence and oncological outcomes. The mean age of first delivery in Finnish Medical Birth Registry varied between municipalities, from 24.4 to 32.5 in 2006–2012 and from 23.7 to 34.5 in 2008–2014. The follow-up of pregnancies lasted only until the age of 22 here and the likely imbalance in age-adjusted fertility rates between study arms may in part explain the observed difference in fertility rates, as in Arms A and B 90% received HPV vaccine, whereas in Arm C 100% received the HBV vaccine.

The preterm birth rates also vary from year to year within and between different municipalities, which could also affect the results. We estimated the PTB rate per all deliveries, not per all women in a given arm, and therefore the differences in fertility rates between municipalities still likely did not affect the observed preterm birth rates.

Worldwide the incidence of preterm birth varies between 5 and 18%, being highest in the developing countries (Blencowe et al., 2012). The overall PTB rate among the non-HPV vaccinated was very low (5.8% among the HBV vaccinated and 4.6% in the non-vaccinated reference cohort), matching the overall preterm rate of 5.2% in Finland (THL, 2018). Offspring of parents with higher socio-economic status might have been more likely to participate in the community-based randomized trial as only half of eligible females consented to participate. This might have contributed to greater age at first delivery, associated with education level (Roustaei et al., 2019), among the participants and lower number of deliveries compared to the non-vaccinated reference cohort here. Also, younger age of the mother has been found to be a risk factor for PTB (Goldenberg et al., 2008). Still, the differences in PTB rates were slightly more pronounced between the HPV and HBV vaccinated only, suggesting perhaps an age-cohort effect in PTB rates, but mainly that the lower PTB rate among the HPV vaccinated was evident also within the randomized cohorts only and that the observed effect cannot be explained fully by selection bias.

4.3. Interpretation light of other evidence

Our data extend the retrospective observational findings (Yuill et al., 2020) to a randomized setting. A cluster-randomized, age-aligned health register-based study is devoid of most inherent biases of retrospective indirect observational studies and suggests that prophylactic HPV vaccination is associated with reduction of preterm births. The observed relative effect of HPV vaccination on preterm birth incidence is far higher here than in the Australian report, reflecting possibly both fundamental differences in study designs and health registration as well as the overall lower numbers of the main outcomes, preterm births, in the current study, possibly contributing to imprecision or more extreme effect estimates.

Even though our results are based on altogether just under 3000 term and 150 preterm deliveries, without nominal statistical significance outside of early preterm birth incidence, the findings are still encouraging. At least 15% of all preterm births are iatrogenic, i.e. resulting from maternal or fetal conditions warranting delivery before term. Spontaneous PTB comprises multiple etiologic pathways and phenotypes including placental dysfunction, hormonal factors and fetal factors (Villar et al., 2012), all unlikely to be affected by the HPV vaccination. On the other hand, occasional findings exist on HPV and placental dysfunction (Gomez et al., 2008), as well as on HPV-positive women being more likely to develop preeclampsia and deliver preterm (McDonnold et al., 2014). Furthermore, not only women treated for CIN, but also women with CIN that has not been treated have higher risk of

subsequent PTB than the general population (Kyrgiou et al., 2016). Still, upper genital tract infections and cervical conizations, excision of the part of the cervix responsible for protecting the uterus from ascending infection, have been suggested to be plausible causal factors for PTB (Frey and Klebanoff, 2016; Habbema et al., 2017; Kyrgiou et al., 2016). Increasing depth and volume of the excised cone as well as repeat treatments have been associated with even higher risk of PTB, suggesting a dose-response effect (Kyrgiou et al., 2016). HPV vaccination reduces both the rates of persistent cervicovaginal HPV infections and development of high-grade CIN lesions warranting treatment (Arbyn et al., 2018), and therefore the number of conizations and upper genital HPV infections, which would fit with our findings on the reduced PTB numbers in HPV vaccinated women.

5. Conclusions

Effective primary interventions to prevent PTB do not exist presently. If our findings are confirmed elsewhere and in the ongoing extended follow-up, the observed effect of prophylactic HPV vaccination reducing PTB incidence would open new lines in research of preterm birth etiology, and lead to public health benefits globally.

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CervarixVR is a registered trademark of the GSK group of companies. EngerixTM is a trademark of the GSK group of companies.

Contributions to authorship

The study was conceived and designed by IK, ML and PN. The data was collated by MG, TE, KA and MH. Statistical analyses were conducted by IK. The data was interpreted, and the manuscript was drafted and revised critically for important intellectual content by all authors. All listed authors had access to full data and meet authorship criteria and no others meeting the criteria have been omitted. PN is the guarantor and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned have been explained.

Declaration of Competing Interest

ML has previously received grants from Merck & Co. Inc. or the GSK group of companies through his former employer, Tampere University. The authors are solely responsible for final content of the manuscript and interpretation. Other authors have no conflicts of interest to declare.

References

- THL, 2018. Parturients and deliveries 1987, 1990, 1995, 2000, 2005, 2010–2018.
- Arbyn, M., Xu, L., Simoons, C., Martin-Hirsch, P.P., 2018. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. *Cochrane Database Systematic Reviews* 5, CD009069.
- Blencowe, H., Cousens, S., Oestergaard, M.Z., Chou, D., Moller, A.B., Narwal, R., Adler, A., Vera Garcia, C., Rohde, S., et al., 2012. National, regional, and worldwide

- estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 379, 2162–2172.
- Frey, H.A., Klebanoff, M.A., 2016. The epidemiology, etiology, and costs of preterm birth. *Semin. Fetal Neonatal Med.* 21, 68–73.
- Gissler, M., Teperi, J., Hemminki, E., Merilainen, J., 1995. Data quality after restructuring a national medical registry. *Scand. J. Soc. Med.* 23, 75–80.
- Goldenberg, R.L., Culhane, J.F., Iams, J.D., Romero, R., 2008. Epidemiology and causes of preterm birth. *Lancet* 371, 75–84.
- Gomez, L.M., Ma, Y., Ho, C., McGrath, C.M., Nelson, D.B., Parry, S., 2008. Placental infection with human papillomavirus is associated with spontaneous preterm delivery. *Hum. Reprod.* 23, 709–715.
- Habbema, D., Weinmann, S., Arbyn, M., Kaminen, A., Williams, A.E., van Kemenade, F., Field, T.S., van Rosmalen, J., et al., 2017. Harms of cervical cancer screening in the United States and the Netherlands. *Int. J. Cancer* 140, 1215–1222.
- Kyrgiou, M., Athanasiou, A., Paraskevaidi, M., Mitra, A., Kalliala, I., Martin-Hirsch, P., Arbyn, M., Bennett, P., Paraskevaidis, E., 2016. Adverse obstetric outcomes after local treatment for cervical preinvasive and early invasive disease according to cone depth: systematic review and meta-analysis. *BMJ* 354, i3633.
- Lehtinen, M., Dillner, J., 2013. Clinical trials of human papillomavirus vaccines and beyond. *Nat. Rev. Clin. Oncol.* 10, 400–410.
- Lehtinen, M., Apter, D., Baussano, I., Eriksson, T., Natunen, K., Paavonen, J., Vanska, S., Bi, D., David, M.P., et al., 2015. Characteristics of a cluster-randomized phase IV human papillomavirus vaccination effectiveness trial. *Vaccine* 33, 1284–1290.
- Lehtinen, M., Eriksson, T., Apter, D., Hokkanen, M., Natunen, K., Paavonen, J., Pukkala, E., Angelo, M.G., Zima, J., et al., 2016. Safety of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in adolescents aged 12–15 years: interim analysis of a large community-randomized controlled trial. *Human Vaccines Immunother.* 12, 3177–3185.
- Lei, J., Ploner, A., Elfström, K.M., Wang, J., Roth, A., Fang, F., Sundström, K., Dillner, J., Sparén, P., 2020. HPV vaccination and the risk of invasive cervical cancer. *N. Engl. J. Med.* 383, 1340–1348.
- Luostarinen, T., Apter, D., Dillner, J., Eriksson, T., Harjula, K., Natunen, K., Paavonen, J., Pukkala, E., Lehtinen, M., 2018. Vaccination protects against invasive HPV-associated cancers. *Int. J. Cancer* 142, 2186–2187.
- McDonnold, M., Dunn, H., Hester, A., Pacheco, L.D., Hankins, G.D., Saade, G.R., Costantine, M.M., 2014. High risk human papillomavirus at entry to prenatal care and risk of preeclampsia. *Am. J. Obstet. Gynecol.* 210 (138.e1-5).
- Romero, R., Espinoza, J., Kusanovic, J.P., Gotsch, F., Hassan, S., Erez, O., Chaiworapongsa, T., Mazor, M., 2006. The preterm parturition syndrome. *BJOG* 113 (Suppl. 3), 17–42.
- Roustaei, Z., Raisanen, S., Gissler, M., Heinonen, S., 2019. Fertility rates and the postponement of first births: a descriptive study with Finnish population data. *BMJ Open* 9, e026336.
- Vanska, S., Luostarinen, T., Baussano, I., Apter, D., Eriksson, T., Natunen, K., Nieminen, P., Paavonen, J., Pimenoff, V.N., et al., 2020. Vaccination with moderate coverage eradicates oncogenic human papillomaviruses if a gender-neutral strategy is applied. *J. Infect. Dis.* 222, 948–956.
- Villar, J., Papageorgiou, A.T., Knight, H.E., Gravett, M.G., Iams, J., Waller, S.A., Kramer, M., Culhane, J.F., Barros, F.C., et al., 2012. The preterm birth syndrome: a prototype phenotypic classification. *Am. J. Obstet. Gynecol.* 206, 119–123.
- Yuill, S., Egger, S., Smith, M., Velentzis, L., Wrede, C.D., Bateson, D., Canfell, K., 2020. Has human papillomavirus (HPV) vaccination prevented adverse pregnancy outcomes? Population-level analysis after 8 years of a national HPV vaccination program in Australia. *J. Infect. Dis.* 222, 499–508.