Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis

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- Editorial: Increased risk of preterm birth after treatment for CIN (*BMJ* 2012;345:e5847)
- Editorial: Adverse pregnancy outcomes after treatment for cervical intraepithelial neoplasia (*BMJ* 2008;337:a1350)
- Read the latest news and research on cervical cancer at bmj.com/specialties/cervical-cancer

STUDY QUESTION What is the impact of cervical excision on fertility and early pregnancy outcomes?

SUMMARY ANSWER There is no evidence suggesting that treatment for cervical intraepithelial neoplasia (CIN) adversely affects fertility, although treatment is associated with a significantly increased risk of miscarriages in the second trimester.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Treatment for CIN increases the risk of preterm birth in subsequent pregnancies, and the risk increases with increasing depth of excision. This meta-analysis found that the risk of miscarriages in the second trimester also increased after excision, although the data suggest no impact on the chances to conceive.

Selection criteria for studies

We searched Medline and Embase and included all studies assessing fertility and early pregnancy outcomes in women with a history of CIN treatment versus untreated women.

Primary outcome

Total pregnancy rates.

Main results and role of chance

15 studies fulfilled the inclusion criteria and were included. The meta-analysis did not provide any evidence that treatment for CIN adversely affected the chances of conception. The overall pregnancy rate was higher for treated women than for untreated women (four studies; 43% *v* 38%, pooled relative risk 1.29, 95% confidence interval 1.02 to 1.64), although the interstudy hetero-geneity was high (P<0.0001). Pregnancy rates did not differ between women with an intention to conceive (two studies; 88% *v* 95%, 0.93, 0.80 to 1.08) and the number requiring more than 12 months to conceive (three studies, 15% *v* 9%, 1.45, 0.89 to 2.37). Although the rates for total miscarriages (10 studies; 4.6% *v* 2.8%, 1.04, 0.90 to 1.21) and miscarriage in the first trimester (four studies; 9.8% *v* 8.4%, 1.16, 0.80 to 1.69) was similar for treated and untreated women, cervical treatment was associated with a significantly increased risk of miscarriage in the second trimester. The rate was higher for treated women than for untreated women (eight studies; 1.6% *v* 0.4%, 16 558 women; 2.60, 1.45 to 4.67).

Bias, confounding, and other reasons for caution

The results should be interpreted with caution. The included studies were heterogenous with regard to their design and included populations. The number of studies and the study size was often small for many of the reported outcomes. All studies apart from one, describe retrospective cohorts that are prone to possible bias. Subgroup analyses for the different treatment methods and for the different comparison groups used were often not possible. An analysis that would stratify according to the depth of the cone or parity was also not feasible.

Study funding/potential competing interests

The study was supported by the Imperial Healthcare NHS Trust Biomedical Research Centre Grant P45272. MK received support and a research award from the British Society of Colposcopy and Cervical Pathology. AM and MK were supported by the Imperial College Healthcare Charity Fellowship. MA was supported by seventh framework programme of DG research of the European Commission, through the COHEAHR Network (grant No 603019); the Institut national du Cancer (Paris, France) through the COSPCC study (Conséquences obstétricales du (sur)traitement des précurseurs du cancer du col utérin) and by the European Federation of Colposcopy. We have no competing interests.

Meta-analysis of studies comparing fertility and early pregnancy outcomes in women after treatment for cervical intraepithelial neoplasia (all types) versus untreated controls

Outcome or subgroup	No of studies	No of women	No with outcome/No in group (%)		Relative risk (95% CI)
			Treated group	Untreated group	
Fertility outcomes:					
Total pregnancy rate	4	38 050	2946/6895 (42.7)	11 906/31 155 (38.2)	1.29 (1.02 to 1.64)
Pregnancy rate in women with intention to conceive	2	70	29/33 (87.9)	35/37 (94.6)	0.93 (0.80 to 1.08)
Conception rates >12 months	3	1348	36/245 (14.7)	102/1103 (9.2)	1.45 (0.89 to 2.37)
Early pregnancy outcomes:					
Miscarriage (total)	10	39 504	350/7660 (4.6)	886/31 844 (2.8)	1.04 (0.90 to 1.21)
Miscarriage (first trimester)	4	1103	51/519 (9.8)	49/584 (8.4)	1.16 (0.80 to 1.69)
Miscarriage (second trimester)	8	2 182 268	258/16 558 (1.6)	8520/2 165 710 (0.4)	2.60 (1.45 to 4.67)
Ectopic pregnancy	6	38 193	114/6985 (1.6)	239/31 208 (0.8)	1.89 (1.50 to 2.39)
Molar pregnancy	2	36 809	50/6267 (0.8)	226/30 542 (0.7)	1.08 (0.80 to 1.47)
Termination of pregnancy	7	38 208	852/6990 (12.2)	2320/31 218 (7.4)	1.71 (1.31 to 2.22)

Risk of preterm delivery with increasing depth of excision for cervical intraepithelial neoplasia in England: nested case-control study

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STUDY QUESTION What is the risk of preterm birth by depth of excisional treatment for cervical disease?

SUMMARY ANSWER The risk of preterm birth is at most minimally affected by a small excision (<10 mm and <1.77 cm^3), but larger excisions, particularly over 15 mm deep or 2.66 cm^3 in volume, are associated with a doubling of the risk.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Several studies have shown an increased risk of preterm delivery after excisional treatment for cervical disease, but the precise role of increasing depth of excision is unclear. One in six births in women who had previously had a large (≥15 mm or ≥2.66 cm^3) excisional procedure at colposcopy were preterm, whereas the risk of a preterm birth among women with small procedures at colposcopy was similar to the risk among those not treated at colposcopy before delivery (about 1 in 13).

Participants and setting

The cohort was women with at least one histological sample taken at colposcopy (at 12 hospitals in England) and a live singleton birth (before or after colposcopy). We identified women with a preterm birth (20-36 weeks) and frequency matched them on maternal age at delivery, parity, and hospital to women with term births (38-42 weeks).

Design, size, and duration

This was a case-control study nested in a record linkage cohort study. From a cohort of 11 471 births, we identified 1313 preterm births and 1313 women with (only) term births. After exclusions, 768 preterm (cases) and 830 term births after colposcopy were available for analysis. We obtained colposcopy details and pathology reports.

Primary outcome(s), risks, exposures

The primary outcome was the risk of preterm birth by depth of excisional treatment of the cervical transformation zone among women who attended colposcopy before delivery. We adjusted relative risks for parity, index of multiple deprivation, maternal age at delivery, and study site.

Main results and the role of chance

The risk of preterm birth was no greater in women with a previous small (<10 mm) excision (absolute risk 7.5%, 95% confidence interval 6.0% to 8.9%) than in women with a diagnostic punch biopsy (7.2%, 5.9% to 8.5%). Those with a medium (10-14 mm; absolute risk 9.6%, 7.7% to 11.5%), large (15-19 mm; 15.3%, 10.5% to 20.1%), or very large excision (≥20 mm; 18.0%, 10.7% to 25.1%) had a higher risk of preterm delivery than those with small excisions. For comparison, the risk of preterm birth in England among the general population is 6.7%.

Bias, confounding, and other reasons for caution

The estimates were robust to several sub-analyses. We had very limited information on potential confounding factors such as smoking. Available data suggest that smoking is unlikely to explain the relation observed between depth of excision and preterm birth, but we cannot exclude it as a confounder. We have no information on treatments from before 1995 and those at non-participating NHS trusts. Some women in the punch biopsy group may also have received ablative treatment. The quality of the birth data submitted to Hospital Episode Statistics has been questioned. Some (17%) births do not have gestational age recorded, and this could affect the absolute rate of preterm births. The dimensions of the excision were missing for 7% of participants and were difficult to determine in those with piecemeal excision.

Generalisability to other populations

Although the relative risk of a preterm birth in treated women overall depends on the quality of colposcopy, relative risks associated with a particular size of excision are generalisable to other colposcopic settings worldwide.

Study funding/potential competing interests

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Relative and absolute risk of preterm birth by depth of excisional treatment in women attending colposcopy before birth

Procedure at colposcopy	No (%) preterm (20-36 weeks)	No (%) term (38-42 weeks)	Relative risk* (95% CI)	Absolute risk (95% CI)
Punch biopsy before birth	210 (27.3)	274 (33.0)	0.96 (0.73 to 1.27)	7.2 (5.9 to 8.5)
Treatment before birth:				
Small excision (1-9 mm deep)	173 (22.5)	223 (26.9)	1 (reference)	7.5 (6.0 to 8.9)
Medium excision (10-14 mm deep)	182 (23.7)	186 (22.4)	1.28 (0.98 to 1.68)	9.6 (7.7 to 11.5)
Large excision (15-19 mm deep)	80 (10.4)	48 (5.8)	2.04 (1.41 to 2.96)	15.3 (10.5 to 20.1)
Very large excision (≥20 mm deep)	54 (7.0)	28 (3.4)	2.40 (1.53 to 3.75)	18.0 (10.7 to 25.1)
Unknown treatment depth	69 (9.0)	71 (8.6)	1.24 (0.86 to 1.79)	9.3 (6.4 to 12.2)

*Adjusted for parity, index of multiple deprivation, maternal age at delivery, and study site.

Stratification of risk for hospital admissions for injury related to fall: cohort study

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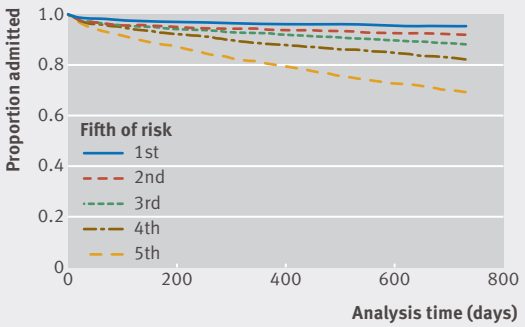
- Research News: Antihypertensives are associated with falls in elderly people (*BMJ* 2014;348:g1736)
- Research: The effect of fall prevention exercise programmes on fall induced injuries in community dwelling older adults (*BMJ* 2013;347:f6234)
- Research: Integration of balance and strength training into daily life activity to reduce rate of falls in older people (*BMJ* 2012;345:e4547)
- Research: Determinants of disparities between perceived and physiological risk of falling among elderly people (*BMJ* 2010;341:c4165)

STUDY QUESTION Can older individuals at high risk for falling after hospital discharge be identified with data available from electronic health records?

SUMMARY ANSWER A logistic regression model based on sociodemographic and clinical features, including a summary measure of burden of adverse effects from drug treatment, can stratify risk for falling within two years of discharge.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Injurious falls represent a preventable contributor to healthcare costs, and adverse effects from drug treatment can increase this risk. A risk score allows higher risk individuals to be targeted for interventions to reduce their likelihood of falling after discharge.

Time to admission for fall by fifth of risk



Participants and setting

The model was developed with 25 924 individuals age ≥40 with an initial hospital discharge. The index admissions were not related to falls. The resulting model was then tested in an independent set of 13 032 inpatients drawn from the same hospital and 36 588 individuals discharged from a second large hospital during the same period. Both hospitals were in New England, United States.

Design, size, and duration

The study utilized a cohort design to examine hospital readmission for injury related to a fall within two years after the index hospital discharge. Data were drawn from electronic health records of the two medical centers. We developed two logistic regression models, one examining sociodemographic and clinical features that would be available at time of discharge only, and a second examining these features plus prior longitudinal course. Both models included a novel measure of total burden of potential adverse effects associated with drugs prescribed at discharge that could be associated with falls. This burden measure sums the frequency of individual adverse effects that could contribute to falls, drawn from published drug labels.

Main results and the role of chance

Among cross sectional features, older age, female sex, white or African-American race, public insurance, greater number of drugs on discharge, greater adverse effect burden score, primary psychiatric diagnosis at admission, and admission via the emergency department were each independently associated with hazard for fall. With the addition of longitudinal measures of illness, including Charlson comorbidity index, the area under the receiver operating characteristic curve was 0.72 in an independent data set drawn from the first hospital system, and 0.71 in the second hospital system. At 80% sensitivity, specificity for fall within two years was 49%. The observed incidence of fall within two years ranged linearly from 4.9% in the lowest fifth of risk to 32.8% in the highest fifth; in all, two thirds of falls were observed among the two highest fifths of risk.

Bias, confounding, and other reasons for caution

While the burden of adverse effect from drugs modestly increases the risk of falls, it does not necessarily follow that interventions dealing with drug treatments will meaningfully reduce risk.

Generalizability to other populations

Generalizability to other US regions, and to non-US populations, must be established. The models incorporate insurance type and race, which could be less predictive in non-US populations, but omission of these features only modestly affected discrimination.

Study funding/potential competing interests

RHP has acted as consultant to multiple biotechnology companies that were not involved in developing interventions to reduce fall risk. Full details are on bmj.com.