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Hello Colleagues,

Somehow, I came across a flurry of pregnancy and SUD recent publications, including a comparison of methadone and buprenorphine on the ¹ and a [new report about cannabis and pregnancy outcomes](#).² Here we'll look at vaping (e-cigarettes, or ECs) in pregnancy. Is it safer than smoking combustible cigarettes (CCs)? Is it safe? Should we be recommending it above NRT?

Pharmacotherapies seem to have less effect in pregnancy than in smokers in general. NRT has shown a minimal benefit, and bupropion no effect. Varenicline has not been studied. ECs are known to be more effective and appealing methods of transitioning away from CCs than NRT in the short term; however, most people who quit CCs will continue to use ECs, therefore remaining nicotine dependent.³ It's not certain what this means for pregnancy or the developing fetal brain. Nicotine is a teratogen in animal studies when administered in chronic high doses, but its safety in human pregnancy, with typical use of nicotine products (other than CCs), is unknown. Previous studies on NRT or vaporized nicotine in human pregnancy show mixed results, ranging from no negative effects to associations with preterm birth and low birth weight.

In RCT, which was a parent trial to this one⁴, there was no difference in CC quit rate between NRT and EC, but there were a lot of crossovers (i.e., many of those assigned NRT used ECs). When the crossovers were excluded crossovers (which introduces some bias), ECs were more effective than NRT in helping pregnant people quit CCs (6.8% ECs vs 3.3 NRT%, $p=0.02$, NNT =29).

*While the question of efficacy in pregnancy remains a bit uncertain, there is still the question of harm. **This study - a secondary analysis of data from the parent study that allows a concentrated look at the people who actually used nicotine products- suggests that vaping nicotine is not worse than using NRT, and it may be safer than CCs.** But messaging⁵ is important. One news outlet summarized this study with the attractive title 'Using e-cigarettes or nicotine patches while pregnant does not harm the mum or baby, new research shows.'^{6,7} This study does not give a free pass to ECs in pregnancy. ECs are not medical products, and this*

data suggests that ECs may help more people transition away from CCs than NRT, but with persistent exposure to nicotine and to vaporized inactive ingredients, both of which may have long-term effects.

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Terms: ECs = ecigarettes, electronic cigarettes, 'vaping'; CCs = combustible cigarettes; nicotine products = ECs or NRT, not CCs

Title: E-cigarettes and NRT have similar short-term pregnancy outcomes when used to achieve abstinence from combustible cigarettes in pregnancy.

Citation: Pesola F, Smith KM, Phillips-Waller A, Przulj D, Griffiths C, Walton R, McRobbie H, Coleman T, Lewis S, Whitemore R, Clark M, Ussher M, Sinclair L, Seager E, Cooper S, Bauld L, Naughton F, Sasieni P, Manyonda I, Hajek P. Safety of e-cigarettes and nicotine patches as stop-smoking aids in pregnancy: Secondary analysis of the Pregnancy Trial of E-cigarettes and Patches (PREP) randomized controlled trial. *Addiction*. 2024 May;119(5):875-884. doi: 10.1111/add.16422. Epub 2024 Jan 17. PMID: 38229538.

Link: <https://pubmed.ncbi.nlm.nih.gov/38229538/>

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The study reviewed here is a secondary analysis of data from a randomized controlled trial on EC vs NRT in pregnancy. In the initial trial there was no difference in CC quits between groups but there was a large number of people in the NRT group who used EC. When those using 'non-allocated' products were removed, EC showed a benefit for CC quit above NRT (6.8% versus 3.6%; RR = 1.93, 95%CI: 1.14-3.26, P = 0.02, **NNT=29**). Further, the EC group had lower frequency of low birth wt (14.8% versus 9.6%; RR = 0.65, 95%CI: 0.47–0.90, P = 0.01). However, there were no difference in birth weight and other outcomes which raises a question about multiple comparisons and the validity of the low birth weight result. Overall, there is the suggestion that EC helps additional people to stop CCs compared to NRT, without a short term difference in safety between NRT and ECs.

This secondary analysis used the same data in a different way to look more closely at the safety of ECs vs NRT *when they are used* in pregnancy. They compared outcomes between those who regularly used NRT vs those who regularly used EC regardless of treatment assigned. This concentrated look at the data can bring out findings not identified in situations where not all were exposed to the therapy (due to high nonadherence), and informs real-world scenarios where people make their own choice to use ECs and NRT.

METHODS

In the initial trial, pregnant women 12-22wks gestation at multiple sites in the United Kingdom (UK) who were daily smokers and motivated to stop smoking were randomized to NRT patches or EC and up to six telephone support calls. Patients were not blinded, nor were those conducting follow up calls, but those analyzing data were. **Patients in both groups were given an initial supply of nicotine product and they could request more for up to 8wks.** After that they were asked to purchase or obtain their own if desired. (Patches are free in the UK). Those in NRT received 15mg/16hr patches and EC patients received 20ml of 18mg/ml tobacco flavored e-liquid and starter kit. They were contacted again at end of pregnancy (EOP, @35weeks gestation) to look for smoking outcomes and for a safety data collection at 3months post-partum.

Regular use of nicotine products was defined as at least 5 consecutive days in wks 1-4, using 'regularly' for at least a week or occasionally for 3 wks or more, or using at EOP. Those using both products were put in the group they mostly used, and if the same, included among EC users.

Salivary cotinine was measured at baseline and at EOP in a subset of participants (those reporting abstinence, >50% reduction and dual use of EC/NRT+ CCs.) CC status and treatment adherence were also assessed by self report post target quit date and EOP. Those with missing data were assumed to be using CCs. Respiratory symptoms were assessed by self report at EOP. Birth and maternal health outcomes were assessed by chart review.

MAIN RESULTS

Follow up: 92% of patients were reached for interview follow up, similar between groups, however salivary cotinine sample collection was low, equal to 49% of those eligible (attempted by mail in). This limited the evaluation of validated nicotine abstinence and reductions so abstinence was measured by self reported 7day point prevalence at EOP.

N= 1138 with the following characteristics:

Table 1 Baseline sample characteristics		
	E-cigarettes (n = 571)	NRT (n = 569)
Age (years), median (IQR)	26.6 (22.5–30.9)	27.3 (23.6–31.1)
Education, n (%)		
Primary and secondary school	229 (40.1)	234 (41.1)
Further education	288 (50.4)	273 (48.0)
Higher education	54 (9.5)	62 (10.9)
Employed, n (%)	274 (48.0)	257 (45.2)
Ethnicity, n (%)		
White British	513 (89.8)	495 (87.0)
Other	58 (10.2)	74 (13.0)
Cigarettes per day, median (IQR)	10 (7–15)	10 (7–15)
FTCD score, mean (s.d.)	4.0 (2.1)	4.3 (2.1)
Cotinine (ng ml ⁻¹) median (IQR) ^a	111 (75.8–165)	118 (73.9–176)
Lives with person who smokes, n (%)	342 (59.9)	328 (57.6)
Past treatment, n (%) ^b		
Chamix	69 (12.1)	79 (13.9)
NRT	268 (46.9)	273 (48.0)
Zyban	7 (1.2)	5 (0.9)
None	272 (47.6)	267 (46.9)
Tried e-cigarettes in the past, n (%)	288 (50.4)	267 (46.9)

FTCD, Fagerstrom test of cigarette dependence. ^aE-cigarettes, n = 529; NRT, n = 531 (cotinine at baseline was missing for 80 participants (7.0%), 53 due to insufficient samples and 27 due to loss at the hospital or in the mail). ^bMore than one treatment could be selected.

Of those, N=1095 had maternal and birth outcomes to evaluate. (n=6 withdrew prior to delivery, n=2 elective termination, n=24 missing outcomes/gave birth outside study site, n=13 twins).

Outcomes

Nicotine Product Use:

Regular use of ECs was more common than regular use of NRT during and at end of pregnancy. Among those who quit CCs, regular EC use was also more common than NRT.

	Regular EC Use	Regular NRT Use	p
During pregnancy	n = 539, 47.3%	n = 235, 20.6%	<0.0001
At EOP	n = 232, 21.2%	n = 28, 2.5%	<0.0001
Among CC abstainers at EOP *	n=131, 67%	n=40, 20.4%	<0.001

* 25 (12.8%) abstainers did not use nicotine products regularly

Among CC abstainers, there were no differences in baseline characteristics by nicotine product use (ie, NRT, EC or no nicotine products). Compared to those who continued to smoke CCs, CC abstainers smoked less initially, had higher educational status and higher employment rate.

Cotinine levels (among the 297 of 607 participants who were planned to have cotinine tested) were reduced from baseline among CC abstainers using ECs. They increased among dual users (using EC and CCs). Among those who self reported >50% reduction in CC, cotinine levels increased in all groups (those using EC, NRT and no nicotine).

Pregnancy outcomes

Birth wt and other adverse pregnancy outcomes among CC abstainers using NRT vs EC didn't differ. (They were combined to be CC abstainers using nicotine, and that group was NOT different than abstainers using no nicotine at all).

Birth wt of abstainers using NRT or EC was slightly higher than those using CCs, 3.3 kg vs 3.1 kg, 95% CI = 0.05–0.25), even after adjustment for baseline differences.

There was no difference in birth weight among those who continued using CCs and dual users (CC+ECs).

Abstainers using no nicotine (n=25) had more preterm birth and related adverse pregnancy outcomes than abstainers using nicotine.

Respiratory symptoms

Collected on n=143. There were no differences in onset of cough, phlegm, SOB or wheeze by use of NRT, EC or non use.

Relapse

1/3rd of those abstinent at 4wks relapsed to use by EOP (6months). There were no differences in relapse whether by use of NRT, EC or non use.

CONCLUSION

In this exploratory analysis, there were not measured baseline differences between pregnant people who used NRT vs EC in their 2nd and 3rd trimester to successfully stop smoking combustible cigarettes (CCs) by the end of pregnancy. People used EC more consistently and for longer duration than NRT but there was no difference in pregnancy outcomes including birth weight or preterm birth, maternal respiratory symptom onset or relapse to CC. Those who did not quit CCs (including dual users ie, CC+nicotine products) had slightly lower birth weight but this could be due to unmeasured confounders or multiple comparisons.

COMMENTARY

This study aimed to understand what the effect of any nicotine product (EC or NRT), is on pregnancy outcomes in by comparing people who used any nicotine product (assigned or not), compared with those who don't. It seems there isn't much difference between the person who successfully uses EC and NRT to quit CCs in terms of baseline characteristics or birth outcomes. It does not tell us anything about the effect of nicotine on the fetal brain in the long term nor does it tell us about exposure to EC vs NRT in the first trimester of pregnancy.

And while one would assume that quitting CCs without nicotine replacement in any form is ideal, note that a very small subset of women (n=25) stopped CCs without any NRT and had more preterm birth and associated outcomes. Likely this was a marker of preterm birth risk where the pregnant person felt motivated to quit and didn't feel comfortable using NRT at all. However, could a quit without nicotine replacement have produced a nicotine withdrawal that made things worse? Not likely and something to act on, but it raises a question.

Some other findings of interest: While those who stopped CC had reduced cotinine from baseline, dual users had increased levels. But being a dual user didn't carry more pregnancy risk than CC alone. This gives some reassurance that continuing to using NRT while using CCs to try to quit isn't doing obvious

And note that relapse within the pregnancy period didn't differ between EC and NRT.

So, what are the limitations to these findings?

Internal validity (how likely are the study results to be what they appear for the study group)

1. The most important limitation is that nicotine product use is not randomized. While attempts were made to account for baseline differences there **may be unmeasured confounders**. It is reassuring that the findings are consistent with the parent study, but that too showed differences only in the more biased study design. In particular this is important when considering the birth weight outcome where those using EC/NRT had higher birth weight than those continuing CCs and the finding itself was isolated.

2. Degree of exposure is a question that may hide differences. Is the similarity btwn NRT and EC because there was not a lot of exposures to those products? The definition for regular use was fairly minimal and only 47% of EC users reported regular EC use that dropped off to 21% by EOP. And only 21% of NRT users reported regular NRT use that dropped off to 2.5% by EOP. Among those who ultimately stopped CCs, the rates are even lower.

In the same vein, nicotine products were only supported for 10 wks and while NRT is free in pregnancy in the UK, ECs are not. This would favor continuation of NRT vs ECs. (Still, more people continued to use EC than NRT.)

3. Abstinence outcomes were self-reported. Could people have been considered CC abstainers who weren't? Yes, but the impact here is probably limited – that misclassification would not likely be different between EC and NRT users.

External validity (can these results be applied beyond the study)

These are patients enrolled in an RCT which generally selects for healthier individuals. Further, it does not focus on people with other SUDs in whom nicotine use disorder shows little response to any intervention. In addition, the UK has better access to care including free NRT in pregnancy so that when NRT ran out it may have been easier to obtain than it would be for many in the US. All of this may mean that any positive effect may be lesser and negative outcomes could be higher given higher baseline risk.

How do we apply this in practice?

We can tell patients *that haven't been able to quit on their own* that its best to stop all nicotine products in pregnancy. If that is not possible, using ECs or NRT to quit CCs does not have glaring short term risks to the pregnancy and may have benefit.

Further, ECs seem to be more readily taken up by patients than NRT perhaps in part because we underdose NRT in pregnancy where renal clearance of metabolites is higher. The similarity between CC and EC use may also make it easier for people to stick with ECs. Either way, it's probably harm reducing to switch from CCs to ECs, remembering that nicotine dependence is still an addiction, and that no study has assessed long term impact of in utero exposure to nicotine.

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