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Appendix

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Appendix to: Bar-Zeev Y, Lim LL, Bonevski B, et al. Nicotine replacement therapy for smoking cessation in pregnancy. *Med J Aust* 2017; doi: 10.5694/mja17.00446 [Epub ahead of print].

Supplemental file 1: Summary of Studies Addressing Safety and Efficacy of NRT in Pregnancy

Study	Year	Aims	Number of participants	Type and Dosage of NRT	Eligibility criteria	Efficacy outcomes	Health and Safety outcomes	Reported adherence
Observational studies – Population based cohorts:								
Dhalwani et al(35)	2015	To assess the relationship between early pregnancy exposure to NRT or smoking with major congenital anomalies (MCA) in offspring	192,498 live births (2001-2012), 2677 exposed to NRT, 9980 smokers, 179,841 control non-smokers	All types of NRT	Women age 15-49 from 570 general practices across the United Kingdom, (covering 6% of the population)	Not reported	OR for MCAs NRT group compared to non-smokers controls 1.12, 99%CI: 0.84–1.48, p=0.31. OR for MCAs NRT group compared to pregnant smokers not receiving NRT 1.07, 99% CI: 0.78–1.47, p=0.58. OR for Respiratory anomalies NRT group compared to non-smokers controls 4.65, 99% CI: 1.76–12.25, p<0.001. OR for Respiratory anomalies NRT group compared to pregnant smokers not receiving NRT 3.49, 99% CI: 1.05–11.62, p=0.07.	Not reported
Brose et al(39)	2013	To assess the association of single and combination NRT with success of quit attempts of pregnant smokers	3880 pregnant women attending stop smoking services (2009-2011), 1166 used single NRT, 2126	Any type	Pregnant smokers trying to stop with the support of 49 English Stop Smoking Services	Using combination NRT (patch plus an oral form) was associated with a higher validated cessation rate (at 4 weeks) compared to not using NRT, adjusted OR 1.93, 95%CI 1.13–3.29, p= 0.016. Using a single NRT was not associated with a higher	Not reported	Not reported

			combination NRT, 588 no NRT		(32% of all services)	cessation rate OR 1.06, 95%CI 0.60–1.86, p=0.84.		
Milidou et al(74)	2011	To investigate the associations between use of NRT and smoking during pregnancy and infantile colic	63,128 live births (1996-2002), 207 exposed to NRT, 15,016 smokers, 1245 to both smoking and NRT, 46600 control non-smokers	Patch/ gum/ Inhaler	Part of the Danish National Birth Cohort, completed two interviews during pregnancy, gave birth to a live singleton	Not reported	OR for infantile colic in NRT group compared to non-smokers 1.6 95%CI 1.0– 2.5, p=0.03. OR for infantile colic in smokers compared to non-smokers 1.3, 95% CI 1.2–1.4. No comparison reported between NRT group and smokers.	Not reported
Lassen et al(38)	2010	To estimate the association between the use of NRT during pregnancy and offspring birthweight	71,320 live births (1996-2002); 1753 used NRT, 15,796 smokers, 53,771 control non-smokers	Patch/ gum/ Inhaler	Part of the Danish National Birth Cohort, completed two interviews during pregnancy, gave birth to a live singleton	Not reported	Mean change in birth weight 0.25 g per week of NRT use 95%CI -2.31, 2.81. Mean change in birth weight when using more than one NRT product in the same week -10.73 g per week of NRT use, 95%CI -26.51-5.05.	Not reported
Strandberg-Larsen et al(37)	2008	To examine whether the use of NRT during pregnancy increases the risk of stillbirth	87,032 pregnancies (1996-2002), 1927 used NRT (of these, 1091 also smoked),	Patch/ gum/ Inhaler	Part of the Danish National Birth Cohort, completed one	Not reported	No significant differences were found in the risk of stillbirth for women using NRT during pregnancy compared to non-users, HR 0.57, 95%CI 0.28–1.16.	Not reported

			13266 smokers that did not use NRT, 71839 control non-smokers		interview during pregnancy, gave birth to a live singleton		Smoking during pregnancy was associated with an increased risk of stillbirth, HR 1.46, 95%CI 1.17–1.82 but Smoking and using NRT was not, HR 0.83, 95%CI 0.34–2.00 (compared with non-smoking women who did not use NRT).	
Morales et al(36)	2006	To examine whether maternal smoking and use of NRT during the first 12 weeks of pregnancy increased the prevalence of congenital malformations	76,768 live births (1997-2003), 250 used NRT, 16812 smoked, 55,915 control non-smokers	Patch/ gum/ Inhaler	Part of the Danish National Birth Cohort, completed one interview during pregnancy, gave birth to a live singleton	Not reported	NRT users had a significantly higher risk for congenital malformations compared to non-smokers; Specifically for musculoskeletal malformations OR 2.63, 95%CI 1.53– 4.52. Excluding minor malformations, the association was not significant For all MCA OR 1.13, 95%CI 0.62–2.07 For major musculoskeletal malformations OR 2.05, 95%CI 0.91– 4.63.	Not reported
Intervention studies:								
Randomized placebo controlled trials								
Coleman et al(40) Cooper et al(49)	2012 2014	To investigate the efficacy and safety of nicotine patches during pregnancy	1050 pregnant women, 521 randomized to NRT group, 529 to control with placebo patches (control)	15 mg/16 hour patch for 8 weeks	12-24 weeks gestation, ≥10 CPD prior to pregnancy, and currently ≥5 CPD, agreed to set a quit	No difference in efficacy from quit date to delivery (9.4% validated abstinence rate in NRT group, 7.6% Placebo group; OR 1.27, 95% CI 0.82–1.98 After one month of treatment significant	All pregnancy and birth outcomes including miscarriage, still birth, mean birth weight, rates of preterm birth, low birth weight, and congenital abnormalities similar in the two study groups. Significantly more deliveries	7.2% in NRT group and 2.8% in Placebo group used patches for more than 1 month

					date	increase in validated abstinence; 21.3% NRT group, 11.7% Placebo; OR 2.1, 95%CI 1.49-2.97.	by caesarean section in the NRT group (20.7%) than in the placebo group (15.3%) OR 1.45, 95%CI 1.05-2.01. Two years after delivery, infants born to mothers using NRT have a significant higher rate of absence of impairment; 73% in the NRT group, compared to 65% in the placebo group; OR 1.4, 95%CI 1.05-1.86, p=0.023.	
Berlin et al(41)	2014	To determine the efficacy of nicotine patches among pregnant smokers, with the Dose individually adjusted according to saliva cotinine levels	402 pregnant women, 203 randomized to the NRT group, 199 to placebo patches (control)	10-30 mg/16 hour patch, dose adjusted based on salvia cotinine level and maintained till delivery	9-20 weeks gestation, ≥5 CPD, motivated to quit	No difference in efficacy from quit date to delivery (5.5% validated abstinence rate in NRT group, 5.1% Placebo group; OR 1.08, 95% CI 0.45–2.6.	Birth weight was not significantly different between the two groups (mean weight NRT group 3065gr (SE 44gr), placebo group 3015 gr (SE 44gr), p=0.41.	Median compliance rate in NRT group 85% (interquartile range 56-99%)
Oncken et al(42)	2008	To estimate the safety and efficacy of 2 mg nicotine gum for smoking cessation during pregnancy.	194 pregnant women, 100 randomized to the NRT group, 94 to placebo gum (control)	2 mg gum, up to 20 a day, substitute one piece for every cig, 6 weeks treatment and 6	≤26 weeks gestation, ≥1 CPD, Did not have to agree to set a quit date	Point prevalence validated abstinence rates similar between the groups at 6 weeks post treatment (13% NRT group, 9.6% placebo group, p=0.45) and at 32-34 weeks gestation (18% vs 14.9%, p=0.56).	Higher birth weight and gestational age in the NRT group: Mean birth weight - NRT group 3287 gr (SD 566gr), placebo group 2950 gr (SD 653gr), p<0.0001. Gestational age - NRT group 38.9 weeks (SD 1.7), placebo	Average days of using the gum was 37.8 days, mean number of gum pieces a day 3.04

				weeks taper.			38 weeks (SD 3.3), p=0.14. Rates of preterm birth and very low birth weight (<2500 gr) were significantly higher in the placebo group compared to the NRT group: Preterm birth - NRT group 7.2%, placebo 18%, p=0.027. Low birth weight - NRT group 2%, placebo group 18%, p<0.001).	
Kapur et al(43)	2001	to examine the efficacy of NRT in reducing smoking among pregnant women who were heavy smokers and who could not quit smoking during their first trimester	30 pregnant women, 17 randomized to the NRT group, 13 to placebo patches (control)	15 mg/ 18 hour patch for 8 weeks, then 10 mg for 2 weeks, and 5 mg for last 2 weeks	12-24 weeks gestation, ≥15 CPD, motivated to quit	Abstinence at 12 week 23.3% in NRT group, 0% in placebo group (p=0.11).	Not reported	59% in NRT group discontinued treatment within first week
Wisborg et al(44)	2000	To assess the effect of nicotine patches on validated smoking cessation in pregnant women and the effect on	250 pregnant women, 124 randomized to the NRT group, 126 placebo patches (control)	15 mg/ 16 hour patch for 8 weeks, then 10 mg for 3 weeks	≤22 weeks gestation, ≥10 CPD	Continuous validated abstinence from treatment to 4 weeks prior expected delivery date 21% NRT group, 19% placebo, RR 1.1 95%CI 0.7, 1.8.	Mean birth weight – NRT group 3457 gr placebo 3271 g; mean difference 186 gr, 95%CI 35-336 gr. Proportion of infants with low birth weight <2500 gr NRT group 3%; placebo group 9%, RR 0.4, 95%CI 0.1, 1.1.	17% of NRT group participants used all 15 mg patches for 8 weeks

		birth weight and preterm delivery					Preterm delivery - NRT group 8%, placebo 10%, RR 0.8, 95%CI 0.4, 1.7.	
Randomized non-placebo controlled trials								
El-Mohandes et al(45)	2013		52 pregnant women, 26 randomized to NRT group plus behavioural counselling, 26 control group (behavioural counselling only)	Based on salivary cotinine levels Either 21 mg/2 wk; 14 mg/4 wk; and 7 mg/4 wk; Or 14 mg/6 wk; and 7 mg/4 wk	<30 weeks gestation, CO ≥8 ppm, or salivary cotinine ≥20 ng/ml, or urinary cotinine ≥100 ng/ml, motivated to quit	Point validated abstinence at end of study NRT group 19%, Control group 0%, p=0.05.	Higher gestational age and birth weight in the NRT group: Birth weight - NRT group 3203gr; control 2997gr, p=0.018. Gestational age - NRT group 39.4; Control 38.4 weeks, p=0.02. No difference in pre-term birth NRT group 4%, Control 8%; or low birth weight NRT group 12%, Control 16%.	Not reported
Pollak et al(46)	2007	To assess whether the addition of NRT to behavioural therapy resulted in improved smoking cessation rates	181 pregnant women, 122 randomized to NRT group plus behavioural counselling, 59 control group (behavioural counselling only)	Choice between patch/gum/ Lozenge; Dosage of patch dependant on smoking level, ranging from 7-21 mg for 6 weeks. Number of gum or lozenge as number of CPD	Smoked >5 CPD Gestational age 13-25 weeks Agreed to set quit date	7-day point prevalence validated abstinence: At 7 weeks post randomization – NRT group 24%, Control 8%, p=0.02. At 38 weeks gestation – NRT group 18%, Control 7%, p=0.04. For every 7 days of NRT use, women were 1.25 times, 95%CI 1.08-1.47, p=0.003 more likely to self-report 7-day point prevalent abstinence.	No difference in mean birth weight or gestational age Birth weight – NRT group 3061 gr (SD=661 gr), Control 3132 gr (SD=688 gr), p=0.51. Gestational age – NRT group 37.9 weeks (SD=3.1), Control 38.6 weeks (SD=2.7), p=0.14. No difference in serious adverse events (after adjusting for previous pre-term labour) – NRT group 27%, Control 18%, Risk Difference=0.09, 95%CI 0.05–0.21, p=0.26.	Use of a mean number of 23.4 patches; or using gum for a mean 8 days; or lozenge for a mean 4 days Secondary analysis published(75) 29% of women used patches for recommended 6 weeks
Hotham et	2006	To assess the	40 pregnant	15 mg/16	Smoked ≥15	Validated abstinence at	Not reported	50% NRT used

al(47)		feasibility of offering NRT patches to pregnant women in terms of acceptability and effects on cessation	women, 20 randomized to NRT group plus behavioural counselling, 20 control group (behavioural counselling only)	hour patch for 12 weeks	CPD, gestational age 12-28 weeks, Interested in quitting	delivery 15% NRT group, 0% Control group.		for 6 weeks or less