

## Research Article

# Smoking Cessation in Pregnancy: Review of Current Strategies

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**Abstract**

Cigarette smoking in pregnancy is a universal problem that compels us to continuously explore different strategies aimed at increasing high quit rates in this population group. Maternal smoking during pregnancy has been linked to increased risk of obstetric and foetal adverse outcomes. Barriers to quitting are multi-factorial and the approach needs to be versatile and patient specific, taking into consideration the dynamics of ethnicity, psychosocial and socioeconomic status.

The aim of this paper is to highlight the different strategies that have been evaluated looking at ways of enabling pregnant women to quit smoking. Furthermore, smoking cessation in special population groups and global initiatives on smoking regulations are discussed. A database search of Ovid Medline, Pubmed, Embase and The Cochrane Library was undertaken to identify relevant articles. Searches were limited to clinical trials in humans and peer-reviewed articles in English Language, and reference lists were searched for other related articles.

A multimodal approach is necessary to increase chances of smoking cessation during pregnancy, this encompasses pharmacological and non-pharmacological measures. The most effective non-pharmacological measures comprise of psychosocial interventions in the form of cognitive behavioral therapy and motivational strategies. In the case of pharmacological approaches, Nicotine Replacement Therapy (NRT) has been the most widely researched with studies showing mixed results in relation to the safety profile in pregnancy. As a result, there is currently no definite consensus as to the safety of NRT in pregnancy, part of the reason being issues with small sample sizes in trials and non-adherence to treatment. To date, Bupropion and Varenicline are not safe to use in pregnancy due to the lack of sufficiently powered randomised trials in the pregnant population. Effectiveness of Nicotine Vaccines in humans is still an area of much needed research.

**ABBREVIATIONS**

WHO: World Health Organization; NRT: Nicotine Replacement Therapy; SES: Socio-Economic Status; CBT: Cognitive Behavioral Therapy

**INTRODUCTION****Epidemiology of cigarette smoking during pregnancy**

It is estimated that more than 1.1 billion people smoked cigarettes world-wide in 2015 [1] and almost 176 million adult females are active daily smokers [2]. According to World Health Organization, the average prevalence of any tobacco smoking amongst females aged 15 years or older in 2015 was 13.1% in

Australia, 18.4% in United Kingdom, 15% in United States of America (USA), 11.3% in Brazil, 10.6% in Japan and 12.2% in Canada [1]. The prevalence of smoking during pregnancy varies from region to region, in Canada, Japan, Germany and Australia it has been quoted to be around 20% [3]. Cigarette smoking amongst pregnant women has been found to be higher in females less than 20 years old and those greater than 35 years old [4].

Studies have shown various characteristics that are predictive of smoking during pregnancy. Maternal demographics that have been linked to increased success of smoking cessation include maternal age, primi-parity, being married or living with a partner, higher level of education and employment status [5-7]. The prevalence of smoking during pregnancy has been established to

be inversely proportional to the level of income [3,4,5,8] Higgins et al assessed "the influence of education on smoking status" in a cohort of 316 participants [9]. The cohort consisted of pregnant women who were still smoking at the beginning of prenatal care and received smoking cessation intervention, and those who were already abstinent and received relapse prevention treatment, both in the form of vouchers [9]. Women with more than 12 years of education were more likely to abstain from smoking at the end of pregnancy compared to those with less than 12 years [9]. Cholinergic Receptor Nicotinic alpha 5 subunit (CHRNA5) is a nicotinic acetylcholine receptor found on Chromosome 15q24, mutation of rs1696998 in CHRNA5 has been reported in previous studies to be associated with decreased probability of smoking cessation [10].

Partners' smoking status and attitudes towards smoking cessation play an important role in the process of smoking during pregnancy [10,11]. Having a partner who smokes confers lower success rates for smoking cessation [10]. The partners smoking activity can act as a trigger for smoking, compounded by having cigarettes being readily accessible [10]. Flemming et al., performed a systemic review of qualitative research looking at partners' views of smoking in pregnancy and in the post-partum period, the results showed that smoking was a "shared and bonding activity" in couples who smoked, therefore making it an important part of the relationship [11]. In addition, participants were found to be more likely to offer support to their pregnant counterparts rather than committing to quitting together [11]. The extent of support provided by the partner is associated with increased chances of quitting [6].

Cigarette dependence determined by the number of cigarettes smoked per day, frequency of urges and the level of expired carbon monoxide, have been reported to be reliable predictors of abstinence, at least in the short period [5].

Low levels of stress and psychiatric comorbidities including Depression and Anxiety have been associated with increased chances of cessation [5]. Up to 12% of pregnant women have Major Depressive Disorder [12,13]. Low socio-economic status and depression have been associated with an increased risk of ongoing smoking during pregnancy [14]. Interestingly and contrary to other previous studies, as well as taking into consideration the variations in study populations, Forray et al., collected data as part of a "Randomised Controlled Trial assessing the efficacy of substance abuse treatment in pregnant women", the colleagues found no statistically significant difference in smoking during pregnancy in the non-depressed versus depressed group [15]. Making a note of the fact that there was reliance on self-reports and the study design was not aimed at assessing smoking cessation [15]. Some studies have suggested that the frequency of stressful events rather than the mood of the pregnant woman was a stronger determinant of smoking [6].

Illicit drug use amongst pregnant women who smoke is another important issue. However, this can be challenging to address given the perceived potential consequences of disclosure [16]. Rates of smoking amongst pregnant women with substance abuse are as high as 90% [12,17]. Urine samples of 115 women participating in a clinical trial for smoking cessation in Burlington, Vermont; USA, were tested for illicit drugs, 53% of participants

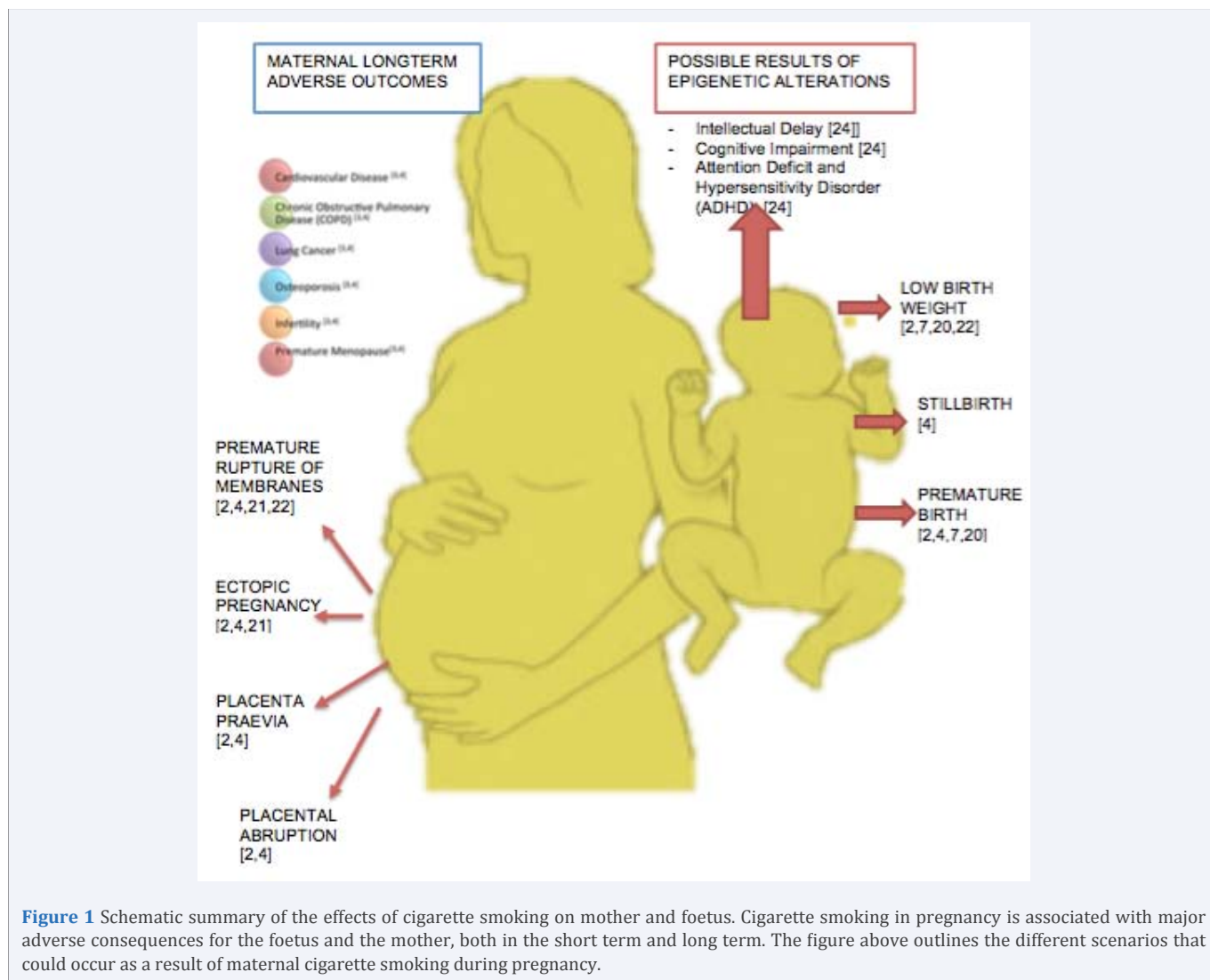
tested positive, with Marijuana being the most commonly used drug accounting for 90% of positive samples. Opioids (18%), Cocaine (5%), Benzodiazepines (3%) and Methadone (3%) were the other drugs that were detected [16].

### Pathophysiology of harm caused by cigarette smoking during pregnancy and associated complications

Constituents of cigarettes that are of most concern because of their recognized adverse effects are nicotine, carbon monoxide, cyanide and lead [4,18]. Nicotine has been shown to cross the placenta, the concentrations were measured in placental tissue, amniotic fluid and foetal serum at different trimesters, the levels in these tissues were found to be higher than in maternal circulation [19,20]. Nicotine was also found to be 88% more concentrated in the amniotic fluid compared to maternal plasma levels in women on nicotine patches [21]. The effects of Nicotine include impaired oxygen delivery resulting in vasoconstriction and abnormal gas exchange within the placenta therefore interfering with nutrient delivery to the foetus [4,7]. Another compound that crosses the placenta is Carbon Monoxide, carboxyhaemoglobin causes a left shift in the oxy-hemoglobin dissociation curve resulting in increased affinity of hemoglobin to oxygen and therefore decreased availability of oxygen to the growing foetus [18].

Foetal complications include stillbirth, premature birth and the associated long term sequelae, and more commonly, low birth weight [2,4,7,20,22]. There are numerous studies that have been conducted aiming at assessing the relationship between smoking during pregnancy and birth weight. The results were varied regarding timing of cessation and effect on birth weight. One of the most recent notable study was by Yan et al., using data from the UK Millennium Cohort Study, the researchers examined the effect of smoking cessation or reduction in smoking intensity at different stages of pregnancy and effect on birth weight [22]. The study demonstrated that mothers who quit smoking by the third month of pregnancy or the end of the first trimester had infants of the same weight as those of non-smokers [22]. It was apparent as well, that the second trimester was the period when most of the deleterious effects of smoking on birth weight occurred [22]. Cessation after the fourth month was linked to significantly lower birth weights [22]. The team demonstrated that mothers who were unable to quit and continued to smoke throughout pregnancy but at a lesser intensity by the third month, managed to give birth to infants of the same weight as those born to persistent light smokers [22]. A population based retrospective study in Ohio comparing women who reported smoking only in the 3 months before conception and those who smoked through the first, second, or third trimester to corresponding group of non-smokers revealed that smoking in the preconception stage was the only time period that did not significantly increase foetal growth restriction risk [23]. Smoking throughout pregnancy carried the highest risk of growth restriction [22].

There is evidence suggesting an association between smoking during pregnancy and some congenital abnormalities, behavioral disorders such as Attention Deficit Hyperactivity Disorder (ADHD), Cognitive Impairment and intellectual delay [2,20,24] as illustrated schematically in (Figure 1). Evidence is



**Figure 1** Schematic summary of the effects of cigarette smoking on mother and foetus. Cigarette smoking in pregnancy is associated with major adverse consequences for the foetus and the mother, both in the short term and long term. The figure above outlines the different scenarios that could occur as a result of maternal cigarette smoking during pregnancy.

emerging regarding the long-term detrimental health effects of maternal smoking on the foetus's long term health, mediated by epigenetic mechanisms [23]. DNA Methylation, Non-coding RNA mediated gene regulation, Imprinting and Histone modification are the four main modes of epigenetic gene regulation, with DNA Methylation being the most well studied [24]. Kiechl-Kohlendorfer et al., found that maternal smoking contributed to delayed psychomotor and mental development in infants based on scores from the Bayley Scales of Infant Development [24,25]. Olds et al examined the relationship between maternal smoking during pregnancy and offspring intelligence at the age of 4, there was evidence that children born to mothers who smoked at least 10 cigarettes per day displayed relative intellectual impairment compared to those children born to mothers who did not smoke during pregnancy [24,26]. Current research has explored the paradigm of a favourable intrauterine environment that is devoid of negative factors such as increased stress levels, exposure to cigarette smoke and viruses resulting in a positive maternal forecast for the foetus [24].

Obstetric complications as a result of smoking during pregnancy range from ectopic pregnancy, placenta praevia,

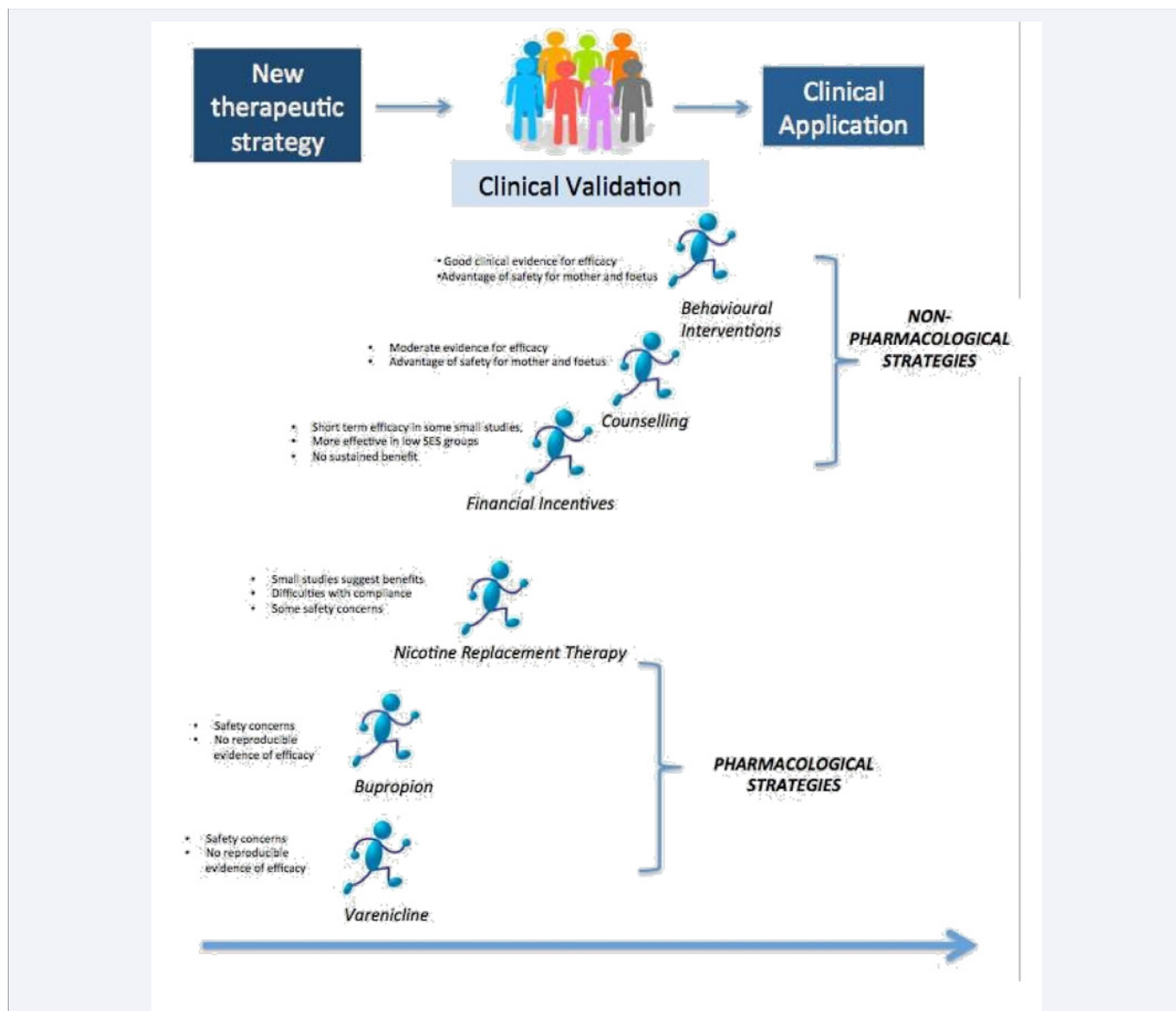
placental abruption and premature rupture of membranes [2,4,21,22].

There is well established evidence on the long-term effects of smoking to the mother including Cardiovascular Disease, Lung Cancer, Chronic Obstructive Pulmonary Disease, Osteoporosis, Infertility and Premature Menopause [3,4].

Given the unquestionable negative effects of cigarette smoking and adverse pregnancy and foetal related outcomes, together with potential economic implications related to this, it is prudent to focus on the best and most effective strategies that are centered around increasing quit rates and hopefully abstinence in the post-partum period.

## METHODS

The aim of this paper was to explore and evaluate available smoking cessation strategies during pregnancy from current literature. A search of electronic databases was undertaken looking into smoking cessation during pregnancy. PubMed search using keywords 'Smoking (MeSH Major Topic) AND Pregnancy (MeSH Major Topic) limited to 'Humans' 'Clinical



**Figure 2** Timeline illustrating relative state of development for therapeutic strategies currently used to promote smoking cessation in pregnancy.

Trials' and 'Review Articles' with 'Free Full Text' in 'English Language', with no limitations to publication dates yielded 25 articles. A further Pubmed search using '(Smoking Cessation) AND Pregnancy' with the same limitations as above yielded 165 articles. Ovid Medline search using keywords 'Smoking Cessation' AND 'Pregnancy', using the 'Map Term to Subject Heading' feature with results limited to 'Review Articles' based on trials in 'Humans' with 'Full Texts' written in 'English Language' yielded 107 articles. Cochrane Library using keywords "Smoking Cessation in Pregnancy" limited to "Cochrane review articles" and unrestricted "Publication Year" yielded 7 relevant papers. Embase search using keywords "Smoking Cessation in Pregnancy" "Full text" in "English Language", "Humans", with no limitations to publication dates, with MeSH selected and 'Smoking Cessation' and 'Pregnancy' as the 'Focus' yielded 66 articles.

A total of 370 articles were retrieved. Following this, review of title and abstract by author BN identified 68 articles that

were deemed relevant to the topic and sufficiently addressed the different aspects of this subject. Hand searching of article reference lists and similar articles yielded a further 7 relevant articles. All the articles were evaluated and the evidence was used to summarize strategies for smoking cessation in pregnancy.

## DISCUSSION

### Interventions to aid cigarette smoking cessation in pregnancy

The rates of smoking cessation have been shown to be higher during pregnancy as most pregnant women are genuinely concerned about the health of their baby [3,4,27]. This provides a unique 'window of opportunity' for health care providers to engage with individuals about smoking cessation and implement effective measures at a time when they are likely to be more receptive and motivated [27]. Various initiatives aimed at smoking



cessation in pregnancy have included non- pharmacological and pharmacological measures. Non-pharmacological approaches incorporate counselling, behavioural interventions, financial incentives and other interventions such as telephone hotlines and internet based programs. Pharmacological strategies comprise of Nicotine replacement therapy (NRT), Bupropion SR and Varenicline.

### Non pharmacological measures

**Counselling and Cognitive Behavioural Therapy:** Brief Counseling sessions complemented by Self Help materials have been shown to significantly increase smoking cessation rates [28,29,30]. Motivational counseling and cognitive behavioral techniques are used recurrently across many studies on smoking cessation in pregnancy, either as a single entity or in conjunction with another therapeutic intervention. Motivational interviewing is designed to encourage the participant to recognise the problem and appreciate the necessity for change, this type of counseling style uses a non- judgemental approach [31]. Studies using Cognitive Behavioral Therapy (CBT) as the mode of therapy have been able to demonstrate statistical differences in average birth weight [7,29].

A meta- analysis of 8 RCTs reviewing the effect of counseling as a single entity in maintaining abstinence at six months in pregnant smokers revealed that the evidence was lacking to suggest that counseling in isolation was efficacious for smoking cessation in the pregnant population, keeping in mind the wide confidence interval of the selected studies [32].

Smoking Cessation and Reduction in Pregnancy Treatment (SCRIPT) is an evidence based education focused intervention program intended for health care providers to use on pregnant smokers [33]. The model focuses on the "5As for Patients Who Are Willing to Quit Smoking" 'Ask-Advice-Assess- Assist-Arrange'. 'Ask' about any use and quantity of tobacco; 'Advice' emphatically for the patient to quit; 'Assess' which stage of quitting the patient is at ; 'Assist' in the process of quitting, 'Arrange ongoing monitoring [30,33,34]. Individuals who attempt to quit on their own have a 5% success rate, however using the 5As model, abstinence rates beyond 5 months are in the range of 15-20% [4]. The 5As model seems to be effective even when delivered in other approaches such as computerized based programs; success was achieved in increasing abstinence in pregnant smokers using the mode of intervention [30]. This model has been widely adopted in multiple cognitive behavioral intervention programs and is supported by the American College of Obstetrics and Gynecology (ACOG), The National Cancer Institute and The British Thoracic Society [4,34].

The "5 R's Intervention" model is for patients who are not ready to quit [35]. Health care practitioners can introduce the 5 R's approach, which aids in identifying the reasons as to why the woman is not prepared to quit smoking [35].

Information retained from face- face interventions can be as low as 5% in the pregnant group [36]. Some women do not wish to attend face-to-face cessation interventions because of time constraints and fear of being judged [28,36]. In this instance, tailored self-help materials in the form of booklets, videos and telephone systems provide an alternative option and

have been shown to increase quitting rates compared to control groups given standard material [28]. The wide confidence intervals in most studies places limitations on interpretation and applicability, therefore more studies are required to convincingly demonstrate that self-help materials are useful in encouraging smoking cessation in pregnancy [28].

Herbec et al., conducted a study exploring the needs and preferences of pregnant women using internet based smoking cessation support systems [37]. Qualitative interviews were conducted on 13 pregnant women on the intervention trial of the Mums Quit study, the researchers found that internet based services were favored more as they were convenient, easily accessible and provided anonymity [37]. The other advantages were the availability of peer to peer communication online which afforded a support structure for the women [37].

Many health care practitioners do not have adequate training to deliver smoking cessation interventions that are effective [35]. Training in brief interventions can be costly and time consuming [30]. Clinicians have mentioned being time poor, limited training and lack of available resources as many of the barriers to providing smoking cessation interventions [7,34,35]. The Association of Women's Health, Obstetric & Neonatal Nurses (AWHONN) developed an evidence -based clinical practice program called Setting Universal Cessation Counseling Education and Screening Standards (SUCCESS) to better educate practitioners about smoking cessation [35].

**Financial Incentives:** Financial or voucher based incentives dependent on abstinence have been shown to be efficacious in smoking cessation [38,39]. These methods are intended to target behavioral processes of reinforcement [38]. Phase II single centre RCT by Tappin et al., demonstrated that financial incentives can motivate pregnant smokers to quit [39]. In the control group, NRT at no personal cost, therapy for 10 weeks and four weekly support phone calls was offered to those who attended a face to face appointment to discuss smoking cessation and also committed to a quit date [39]. The intervention group received the same offer with the addition of £400 of shopping vouchers divided over a specified period of time contingent on maintenance of abstinence [39]. The results showed that more smokers in the incentives group, 69 (22.5%) versus 26 (8.6%) compared to the control group had successfully quit smoking [39]. Controlled trials have shown that 'voucher-based contingency management' for smoking cessation during pregnancy improved birth weight, the difference in birth weight between the incentive group and controls was around 200 to 210g [38].

Financial rewards seem to be more effective in persuading low income pregnant women, unfortunately, financial incentives have not been shown to enhance long term quit rates, the success dwindles down when the rewards are no longer offered [4].

**Ultrasound-guided feedback:** A prospective randomized trial of 360 women between 16 -26 weeks' gestation was performed assessing the efficacy of adding personalized feedback during ultrasound [31]. The cohort was divided into three groups: 'best practice' which was the 5As strategy, "best practice in combination with ultrasound feedback" or "Motivational Interviewing-based counseling plus ultrasound feedback" [31].

At the end of the pregnancy, a higher proportion of women who were in the motivational and Ultrasound group were abstinent (18.3%) followed by “Best practice plus ultrasound feedback” group (14.2%). However, the results were not statistically significant, and interestingly, women who smoked >10 cigarettes per day were unaffected by the intervention [31].

**Telephone hotlines:** Social Support tools such as telephone hotline numbers and group sessions have shown efficacy in the general population but the same results have not been replicated in the pregnant population [4]. This highlights the uniqueness of this cohort and the importance of investing more research focused on exploring the complexities of barriers to smoking cessation in this particular group of smokers.

**Exercise:** Studies have shown that a single session of exercise in non-pregnant smokers reduced tobacco cravings and withdrawal symptoms [40]. Ussher et al conducted a randomized control trial to ‘determine the effectiveness of physical activity for smoking cessation during pregnancy’ [41]. 789 pregnant women from 13 hospitals in England were recruited, the control group was allocated to weekly behavioral support sessions for smoking cessation and the intervention group had supervised treadmill exercise and physical activity consultations in addition to the weekly support sessions [41]. There was no statistical difference in the rates of smoking abstinence at the end of the pregnancy between the two groups [41]. Prapavessis et al., studied 15 women in their second trimester who had been abstaining from smoking, the team evaluated the effect of exercise in the form of 20-minute treadmill walk on cravings and withdrawal symptoms, what became apparent from the passive state control randomized study, was that exercise diminished cravings in the immediate period and within 10mins post exercise, conversely, this was not to a statistically significant degree with regard to withdrawal symptoms [40].

As the pregnancy progresses, exercise is less likely to be a viable option to curb cravings for the pregnant woman, meaning that alternative effective therapies would have to be employed. The usefulness of exercise in heavy smokers is also an area of interest.

When it comes to non-pharmacological interventions, there has been a plethora of studies exploring different measures that can be used to encourage pregnant smokers to quit. Small sample sizes and wide confidence intervals have affected the reliability and applicability of some of the studies. The search for more innovative strategies should continue to be relentless, it is also evident that no single measure is effective on its own, thereby necessitating the need to continue exploring multi-modal strategies, and lastly investigating reasons for low recruitment rates.

### Pharmacological measures

Despite various smoking cessation strategies, literature shows that up to 20-25% of pregnant women will continue to smoke throughout pregnancy [21]. CBT is effective in pregnancy; however, the success rate is lower in women who smoke more than 10 cigarettes a day, categorizing them as heavy smokers [42]. Some women may require pharmacological measures in addition to counseling and cognitive behavioral therapies to achieve

success with smoking cessation or reduction [32]. There are three pharmacological agents that have been approved for smoking cessation in non -pregnant populations; these are Nicotine Replacement Therapy (NRT), Bupropion SR and Varenicline. Of these three interventions, there is conflicting recommendations about the use of NRT in pregnancy; furthermore, Bupropion SR and Varenicline are not routinely used due to safety concerns in pregnancy and lack of compelling evidence with regard to efficacy in pregnancy [43].

**Nicotine Replacement Therapy:** Nicotine is metabolised by the liver via the CYP2A6 enzyme, Flavin containing mono-oxygenase and UDP – glucuronosyltransferase [44]. There are various elements that influence how nicotine is metabolised, these include genetic factors, gender, ethnicity, age, diet, pregnancy and kidney disease amongst other things [44]. Nicotine works by increasing dopamine release resulting in feelings of pleasure, thereby emphasizing the positive sensations associated with smoking and reinforcing the addictive behaviour [7]. Nicotine replacement is effective in the general population and is easily accessible [42], in smoking cessation it works by reducing cravings and withdrawal symptoms [18]. Pregnancy is associated with changes in metabolism and can affect pharmacokinetic processes of drugs, for example, there is increased clearance of nicotine by up to 60% in pregnancy [44,45]. These physiological changes need to be taken into consideration when assessing the efficacy of types of NRT in this group [44].

Compared to cigarettes, which consist of multiple other toxins that could potentially have adverse effects on the foetus, nicotine is a pure form of replacement and theoretically is expected to be relatively safer [46,47]. Nicotine is available in various formulations ranging from transdermal patch, lozenges, gum, nasal spray, nicotine inhaler, and sublingual tablets [7,44,48]. Previous trials have yielded inconsistent results on the safety of NRT in pregnancy [32], small sample sizes, non-adherence to therapy, have been some of the challenges encountered. Coleman et al did not show any increased risk of adverse outcomes during pregnancy or birth with the use of nicotine patch 15mg/16 hours, however low compliance rates limited the reliability of the conclusions drawn from the randomized control study [49]. A meta-analysis of 6 trials of NRT in pregnancy did not show any significant statistical difference in terms of rates of miscarriage, stillbirth, low birth weight, premature birth or neonatal death in mothers treated with NRT versus untreated ones [6,21].

Cotinine levels are used in most studies of nicotine replacement to assess the amount of nicotine exposure [48]. Nicotine patch has been found to reduce cravings better than nasal spray [48]. Cotinine levels generated from 15mg/16 hours’ nicotine patch during pregnancy have been found to be lower compared to levels from cigarette smoking [47]. This may be part of the reason for lack of effectiveness of nicotine replacement therapy in some pregnant women as the amount of nicotine delivered is less than what they are used to. This may also be a contributing factor to non-adherence especially if the women feel that the NRT is not helping with cravings. On the other hand, this may suggest that NRT might be safe in pregnancy as the levels that the foetus is exposed to are not as high as with cigarette smoking. The main limiting factor with regard to assessing this postulation

is the ongoing issue with low compliance with NRT in the trials suggesting that the adverse outcomes of the use of nicotine patch can potentially be underestimated [21,43] because the treatment is not tested for long enough to conclusively reach a consensus. Moreover, small sample sizes resulting in underpowered studies is another challenge.

Despite lack of consistent evidence on the safety and efficacy of NRT in pregnancy some countries recommend its use, for example the United Kingdom and France recommend NRT in pregnancy, whereas the United States of America guidelines have not recommended NRT use in smoking cessation in pregnancy [32,46,50,51]. Usually NRT is used in pregnant women with moderate to high dependence whom behavioural interventions alone were not effective [6,43], it should be with caution and mothers should be made aware of the unknown risks and uncertainties surrounding nicotine therapy in pregnancy [4,21,32]. The lowest dose possible, required to provide abstinence and control cravings should be used [21]. Intermittent dosing in the form of nicotine spray or gum may be safer compared to nicotine patch which provides continuous dosing [7,21,43,48].

The Smoking, Nicotine and Pregnancy (SNAP) trial was a large randomised controlled trial involving 1050 participants, comparing NRT in the form of a patch (15mg/16hrs) with transdermal placebo to investigate if NRT would increase smoking cessation in pregnancy without adversely affecting the infant [52]. The outcome of the study showed that there were no significant rates of abstinence between the two groups and no significant difference in average birth weight, however compliance with treatment in both groups was still a problem as has been in previous smaller studies, affecting interpretation of the results [52]. In addition, a follow up of the SNAP trial demonstrated that offspring born to mothers who used NRT during pregnancy had no impairment in terms of development and behavioural problems at the age of 2 years compared to the placebo group [53].

**Nicotine Vaccines:** Nicotine vaccines are intended to stimulate the body to produce antibodies which would then bind nicotine and prevent it from crossing the blood- brain barrier, therefore preventing re-enforcement feedback that forms part of the addiction [18,51,54]. There was a promising phase II trial suggesting abstinence duration of up to 1 month, however subsequent two phase III trials did not affirm the findings from the phase II trial [51,54].

**Bupropion SR:** Bupropion's effectiveness and safety in pregnancy is uncertain [12]; evidence to support its use in pregnancy is lacking [21,43,46]. It was first approved in the USA as an atypical antidepressant [51,55]. Its mechanism of action is thought to be via inhibition of dopamine and noradrenaline [12,43,46,51], it also acts as a weak nicotine receptors blocker [18,51]. Bupropion works by mainly relieving withdrawal symptoms [18]. The advantage of Bupropion is that there is no nicotine exposure to the foetus however the effect on the foetus is unclear [4,21].

**Varenicline:** Varenicline is thought to have two mechanisms of action, the first being as a partial agonist at the alpha4beta2

acetylcholine receptors and the second by blocking the action of nicotine at the same receptors [51,55]. Based on this mechanism of action, it can potentially relieve withdrawal symptoms and reduce the positive feedback from smoking relapse [18,51]. Varenicline appears to be safe in the general population, however its safety in pregnant and lactating women is not yet known and the evidence is insufficient [21,43,46,51].

**Pharmacotherapy in Pregnancy:** The US Preventive Services Task Force (USPSTF) has no recommendations on the use of pharmacotherapy for smoking cessation in pregnancy [42,56]. The general agreement is that the evidence is lacking on the benefits of NRT, Bupropion SR, or Varenicline to achieve tobacco cessation in pregnant women or to improve perinatal outcomes [45,56]. This is because of lack of good consistent evidence based material, making it difficult to reliably determine the benefits versus harm of pharmacotherapy in this population.

The Therapeutic Goods Administration (TGA) pregnancy categorisation system used in Australia places NRT, Bupropion and Varenicline in different categories for drugs used in pregnancy [57]. NRT is in Category D, which are "drugs that have caused, are suspected to have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage" [57]. Varenicline is in Category B3 which are "drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans" [57]. Bupropion is Category B2 and these are "drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage" [57].

### Special population groups and most effective smoking cessation strategies

**Depression and smoking:** Compared to non - depressed women, depressed women have been reported to be four times more likely to smoke during pregnancy [7].

Chisolm et al assessed the effect of Citalopram/Escitalopram versus Bupropion on cigarette use in a group of depressed pregnant women on a comprehensive drug treatment program for substance abuse including opioids, cocaine, alcohol and/ or marijuana [12]. The study also compared each group of women to their non-depressed counterparts who did not require antidepressants [12]. Despite small sample sizes and other limitations to the study, the results showed a tendency towards less cigarette use in the Bupropion group compared to citalopram/ escitalopram group despite similar effective drug doses [12]. In addition, the decrease in cigarette use in the Bupropion group was similar to that in the non-depressed group [12]. It is worth mentioning, that the average Bupropion dose used in non -pregnant individuals to achieve smoking cessation



response was not tested in this study. Also the Bupropion users appeared to have had better mood ratings compared to citalopram/escitalopram group [12], it is unclear whether this may have, in any way contributed to the decrease in cigarette use. Depression focused treatment programs could potentially help pregnant smokers with high levels of depression in terms of reduction of depressive symptoms and enhanced abstinence [14].

Dornelus et al., also reviewed the response to smoking cessation with the use of nicotine gum in a group of pregnant women with Major Depression and Post Traumatic Stress Disorder (PTSD) [59]. The randomised placebo controlled trial of 194 low income and ethnically diverse participants, showed no difference in response to treatment between the group assigned to nicotine gum versus placebo gum [59].

**Indigenous Groups:** Despite falling incidence rates of smoking in the general population, statistics show that tobacco smoking in Indigenous community still remains high [7,59]. In Britain, smoking prevalence is variable according to ethnicity and gender, for example Irish men and women, Bangladeshi and Black Caribbean communities have higher rates of smoking compared to the average population [60].

Patten et al carried out a Pilot study on American Alaskan pregnant women living in Yukon-Kuskokwim who smoked cigarettes and chewed tobacco in the form of Iqmik [61]. The control group was randomized to 5 minute face- face counseling using the 5As model and four 'pregnancy and culturally specific brochures', while the intervention group received the cessation guide and 15-25 minute of counseling using the 5A model, followed by the pregnant woman watching a Video that had been put together by local Native people addressing the adverse effects of tobacco use during pregnancy, including stories of Alaskan women who quit smoking during pregnancy, so to serve as role models [61]. The counselor would then discuss the video, and also educate the woman on cessation skills, and give the woman the video to take home and view with her family [61]. Despite high initial recruitment numbers, ultimately the participation rate was low, this therefore affected assessment of the intervention with regard to abstinence outcomes. However, there were important points highlighted from this pilot study, one of them being that, when it comes to certain cultural groups, it is imperative, to in- cooperate the local community when coming up with interventional strategies and people whom the target group can identify with. Addressing cultural beliefs about tobacco smoking during pregnancy and providing education about safety is also important, for example in this study, some women had been under the impression that Iqmik was safer in pregnancy compared to other tobacco products [61]. This perception was thought to be one of the reasons for low participation, in addition to this misconception, lack of time and not being ready to quit were some of the reasons cited by the women for lack of participation [61]. The BOABS study "Be Our Ally Beat Smoking" [59] was a randomized controlled trial focused on Aboriginal and Torres Strait Islanders in a remote Australian community, although this study was not in pregnant women, it still highlighted similar points raised by Paten et al with regard to delivering culturally specific programs and

involving indigenous local community members as part of the strategy. Low participation rates were still an issue, resulting in difficulty powering the study [59].

**Low Socio-Economic Status:** Low socioeconomic groups have previously been shown to have high rates of cigarette smoking in pregnancy [7]. Over the years, the prevalence of smoking in the United Kingdom has declined, however there is marginal change in low income groups overall [60]. Wen et al., studied low income inner city pregnant women who received either standard or highly intensive quit smoking counseling program [62]. The results showed that in the prenatal phase, non-adherence was predicted by a greater number of cigarettes smoked; in the postpartum follow-up phase, non-attendance was predicted by lower educational level [62]. Appreciating the dynamic reasons that contribute to low attendance rates at counseling sessions will assist in identifying women who would otherwise be at risk of non-adherence and therefore guide implementation of appropriate effective measures to this particular group [62].

Essex et al found that NRT plus behavioral intervention was slightly more expensive than behavioural support alone, with the cost mainly being due to the patches [63]. However, there was a higher quit rate in the NRT group, taking into account the wide confidence interval limiting statistical interpretation of the results [63]. This introduces the debate of whether it is worthwhile for government agencies to invest in at least subsidising NRT if it helps to facilitate smoking cessation in pregnancy especially in the setting of women from low socioeconomic background, more-so that it has been established that this group is the most vulnerable when it comes to smoking during pregnancy.

**Adolescents:** More than 80% of long-term smokers start smoking before the age of 18 years old [51,60]. According to World Health Organization (WHO) Report on the Global Tobacco Epidemic, 2013, as a result of exposure to tobacco advertising, promotion and sponsorship, one third of youth experiment with tobacco [64]. During 2007 to 2014, the prevalence of tobacco use in the female 13-15 age group was 8.3% globally [1]. According to the U.S. Department of Health and Human Services, the proportion of high school students who smoke is around 18% [65]. Although these figures are significant, the rate of adolescent cigarette smoking has fallen over time [66], anti-smoking initiatives have contributed to decreasing rates of smoking in adolescents [66,67]. For example, in New South Wales, Australia, the percentage of adolescents reported as current smokers was down to 6.7% in 2014 compared to 23.5% in 1996 [67].

Evidence is lacking regarding behavioral measures that are most effective in encouraging smoking cessation in the younger population [60]. In saying that, mass media campaigns aimed at discouraging tobacco use combined with other interventions have had an impact on the reduction of the number of youth who take up smoking [55]. In addition, raising Taxes has been found to be effective in reducing tobacco use especially in low income groups and adolescents [1,67-69].

A decline in the prevalence of smoking in adolescents will hopefully result in diminished burden of tobacco use in the general population and in turn less women in the reproductive age who smoke.



## Tobacco regulation policies and effect on birth outcomes

Historically, as a strategy to appeal to women and girls to smoke cigarettes, Tobacco companies have created images of women who smoke to be “emancipated, sophisticated, glamorous, attractive and slim” amongst other theoretically desirable traits [1,3].

In 2008, the World Health Organization introduced MPOWER, which consist of six comprehensive measures aimed at facilitating the implementation of the goals from WHO Framework Convention on Tobacco Control [1,55]. These measures include “Monitoring of tobacco use and prevention policies; Protecting people from tobacco use; Offering help to quit tobacco use; Warning about the dangers of tobacco use; Enforcing bans on tobacco advertising; Raising taxes on tobacco promotion and sponsorship.” [1,55].

Increasing Taxes on Tobacco has been correlated with improved birth outcomes as a result of a decline in the number of women who smoke prenatal [68]. Increasing cigarette prices due to increased taxes, has had a positive effect in terms of reducing the demand for cigarettes [69] in both high income and low-middle income countries [55]. However the effect seems to be more pronounced in low income countries, for example, it is estimated that in high income countries, a 10% increase of cigarette costs would result in a decrease of up to 5-10% in the demand for cigarettes compared to 4-14% in low to middle income countries [55]. A few studies have evaluated the effect of increasing cigarette prices on the consumption by pregnant women, overall this attempt has been shown to reduce the prevalence of smoking in this population group [55]. There have been regulations on tobacco packaging and labelling to include conspicuous warning messages for consumers [1,55]. Graphic pictures on cigarettes packaging are meant to dissuade potential young consumers from taking up the habit and at the same time increase the chances of quitting by current smokers [1].

Media campaigns aired on television are amongst many strategies employed to educate the general population on the adverse health effects of cigarette smoking [69]. It has been hypothesised that enforcing bans on tobacco advertising or sponsorship could reduce consumption by approximately 7% or higher in some countries [1]. Comprehensive bans have been shown to be more effective in reducing cigarette consumption [55].

Prohibiting sale of tobacco to minors and enforcing the law via random inspections of retailers and enforcing substantial fines is another approach to deterring smoking in younger groups [4,67,69]. Yan determined that increasing the cigarette purchase age to 21 correlated with reduced prenatal cigarette use by 15% and also lowered the proportion of infants born underweight by 19% [70].

Restricting smoking in public arenas and work places in turn reduces exposure to second hand smoking [55,69]. There seems to be conflicting evidence regarding the relationship between foetal outcomes and exposure to second hand smoking mainly as a result of the quality of studies and potential confounders [68,71,72]. Been et al reviewed studies focusing on association

between bans on smoking in the work place and/or public areas and foetal outcomes. Smoke free regulations were linked with decreased preterm births, however there was no substantial difference in low birth weight [73]. Zubair et al., found a reduction in the small for gestational age birth rates after conducting a cross-sectional retrospective study analysing birth weights between 1999 to 2008, post implementation of comprehensive banning of smoking in the workplace in Ireland in 2004 [74]. On the other hand, Hankins et al did not find any considerable effect of smoking bans on neonatal health [75]. Robust consistent evidence on the direct impact of second hand smoking on foetal outcomes is yet to be established, in saying that, the results of the current studies demonstrate that initiatives aimed at reducing exposure to second hand smoking do have a positive effect, which is encouraging.

## CONCLUSIONS

Smoking during pregnancy is an indiscriminate problem and affects women from all backgrounds. The deleterious effects of smoking in pregnancy are undeniable and have both short and long term consequences for the woman and the foetus. With regards to timing of cessation and effect on birth weight, it is evident that quitting within the first trimester results in much better outcomes [22] and therefore interventions should focus on early smoking cessation with efforts dedicated to the first trimester.

Evidence shows that it is imperative to implement culturally adapted measures when developing interventional programs for minority and certain ethnic groups. Reasons for low participation rates in trials need to be explored further.

It is crucial that we uncover techniques that are effective in facilitating smoking cessation in pregnancy especially given the economic burden associated with premature births. The use of pharmacological measures is still contentious, particularly with regard to NRT. There is insufficient evidence to support Bupropion SR and Varenicline use in pregnancy to date. More randomized controlled trials with greater sample sizes and better adherence rates are needed to assess the safety of pharmacotherapy in pregnancy.

A decline in the incidence and prevalence of smoking in the general population could possibly in turn result in less women who smoke, therefore less pregnant smokers. Preventive strategies that have been found to be most effective in reducing prevalence of cigarette smoking were prohibiting smoking in public arenas and increasing tobacco taxes [69]. Higher tobacco taxes had a significant effect on diminishing smoking rates in adolescents and low income groups [1,66,67,69]. In addition to enforcing other initiatives such as comprehensive banning of tobacco promotions and advertisements, restriction of sale of tobacco to minors, enforcing appropriate labelling of tobacco products; ongoing efforts should be focused on coming up with more innovative strategies aimed at reducing cigarette smoking in vulnerable groups which include women from low SES.

An individualized approach is what has been shown to yield the highest degree of success for cigarette smoking during pregnancy, with motivational counseling and behavioral interventions generating better success rates and safety profile.

With regard to women who are heavy smokers, whom behavioral therapies alone are frequently inadequate to ensure smoking cessation, more research is required, focused especially on exploring alternative pharmacological therapy that would have negligible adverse effects on the foetus.

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