



Facilitators and barriers to substance-free pregnancies in high-income countries: A meta-synthesis of qualitative research



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ABSTRACT

Background: Previous studies have associated substance use (alcohol, illicit drugs and smoking) to negative pregnancy outcomes, including higher risk of stillbirth.

Aim: This study aims to identify facilitators and barriers reported by women to remain substance free during pregnancy.

Methods: A systematic search was conducted in six databases from inception to March 2019 and updated in November 2020. Qualitative studies involving pregnant or post-partum women, from high-income countries, examining women's experiences of substance use during pregnancy were eligible. Meta-ethnography was used to facilitate this meta-synthesis.

Findings: Twenty-two studies were included for analysis. Internal barriers included the perceived emotional and social benefits of using substances such as stress coping, and the associated feelings of shame and guilt. Finding insensitive professionals, the lack of information and discussion about risks, and lack of social support were identified as external barriers. Furthermore, the social stigma and fear of prosecution associated with substance use led some women to conceal their use. Facilitators included awareness of the health risks of substance use, having intrinsic incentives and finding support in family, friends and professionals.

Discussion: Perceived benefits, knowledge, experiences in health care settings, and social factors all play important roles in women's behaviours. These factors can co-occur and must be considered together to be able to understand the complexity of prenatal substance use.

Conclusion: Increased clinical and community awareness of the modifiable risk factors associated with substance use during pregnancy presented in this study, is necessary to inform future prevention efforts.

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Statement of significance

Problem

Substance use during pregnancy is a major contributor to adverse pregnancy outcomes, including stillbirth.

What is already known

Although there is evidence of the risk of smoking, drinking and using illicit substances during pregnancy, there are some women who continue to engage in these behaviours during pregnancy.

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What this paper adds

Stillbirth prevention strategies in high income countries should focus on modifiable risk factors. This paper provides further evidence to improve understanding of the complexities and factors affecting the use of substances during pregnancy.

1. Introduction

Prenatal smoking, consumption of alcohol and illicit drug use are significant public health concerns with important implications for women and infants [1]. Smoking, consuming alcohol and using illicit drugs during pregnancy are well established risk factors for a wide range of adverse pregnancy outcomes [2]. These include an increased risk of miscarriage [3], ectopic pregnancy [4], placental pathologies [5], low birth weight [6], small for gestational age [7], intrauterine growth restriction [8], preterm delivery [7], fetal alcohol syndrome [9], and neonatal death [3]. Prenatal smoking, alcohol consumption and illicit drug use are also associated with an increased risk of stillbirth [3,10,11].

The occurrence of stillbirth differs across countries. In 2008, 2.65 million stillbirths were estimated worldwide, with 98% of them occurring in low-income and middle-income countries [12]. In 2015, the rates of stillbirth per 1000 births at 28 weeks gestation or more in high-income countries varied from 1.3 in Iceland to 8.8 in Ukraine [13]. However, it is difficult to compare rates of stillbirth amongst countries due to the variability in the definitions used and the under-reporting of stillbirths under 28 weeks gestation.

In a systematic review and meta-analysis of 142 studies published in 2015, any active smoking and second-hand smoke exposure during pregnancy were associated with a higher risk of stillbirth (Standardised Rate Ratio (sRR) 1.46 and sRR 1.40 respectively) [3]. Previous studies have also associated heavy consumption of alcohol with an increased risk of stillbirth [14,15]. Aliyu et al. concluded in their retrospective cohort study with more than 650,000 pregnancies, that the likelihood of stillbirth between 20 and 28 weeks gestations was higher in women who drank alcohol [15]. According to this study, women consuming five or more drinks per week during pregnancy experienced a 70% increase in the risk of stillbirth. Women consuming 1–2 drinks per week had a hazard ratio of 1.5 (95% confidence interval 1.0–2.1), no increase in risk amongst women drinking 3–4 drinks per week, and a peak increase in women drinking 5 or more drinks per week. In terms of illicit drug consumption, Varner et al. concluded that a positive test for any illicit drug in the umbilical cord homogenate was associated with an increase in the risk of stillbirth at 20 weeks gestation (OR 1.94) [17]. A recent meta-analysis reported that the global prevalence of smoking during pregnancy was estimated to be 1.7% [18]. This study concluded that the highest prevalence of smoking during pregnancy was in the European Region (8.1%) and the lowest in the African Region (0.8%) [18]. The five countries with the highest estimated prevalence of smoking during pregnancy, regardless of frequency or quantity, were Ireland (38.4%), Uruguay (29.7%), Bulgaria (29.4%), Spain (26.0%) and Denmark (25.2%) [18]. However, previous studies have reported variations in prevalence, such as a prevalence of 11 to 17% of smoking among pregnant women in Ireland [19,21]. Prevalence of prenatal alcohol consumption has been found to be higher than that of smoking. A systematic review and meta-analysis published by Popova et al. concluded that, globally, 9.8% of women consumed alcohol during their pregnancy [22]. The highest prevalence was observed in the

European World Health Organization Region (25.2%), whereas the lowest was in the Eastern Mediterranean WHO Region (0.2%). The five countries with the highest estimated prevalence of alcohol use during pregnancy were Ireland (60.4%), Belarus (46.6%), Denmark (45.8%), United Kingdom (41.3%) and Russia (36.5%).

Cocaine, amphetamines, opioids, marijuana, hallucinogens and toluene-based solvents are the illicit drugs that have been found to be most commonly used by pregnant women [23,24], however, establishing the prevalence of illicit drug use in pregnant women may be more difficult than for alcohol and smoking. For example although social stigma can exist for all of these behaviours during pregnancy, legal repercussions associated with substance use might drive some women to avoid disclosure [24,25]. However, in the 2010 National Survey on Drugs and Health conducted among pregnant women aged 15 and 44 in the USA, it was reported that 4% of pregnant women were current illicit drug users [26].

Understanding women's attitudes, perceptions and experiences of substance use is essential to obtaining insight into the facilitators and barriers that modulate these behaviours during pregnancy. Qualitative research is a useful approach in this regard to explore and understand the nature and interaction of the different layers of the studied phenomenon while maintaining the particular complexities of human behaviour [27]. To date a number of primary qualitative studies have been conducted to understand women's prenatal smoking, alcohol and illicit substance consumption [28–37] and we found three meta-synthesis exploring experiences of women who commence pregnancy as smokers [38–40]. However, no prior meta-synthesis has been conducted related to the other types of substances used during pregnancy.

The aim of this meta-synthesis is to analyse and synthesise all of the evidence drawn from qualitative research to date in order to identify facilitators and barriers to a substance-free pregnancy in high income countries. This will facilitate developing in-depth insights and understandings of these prenatal health behaviours [41,42]. By identifying barriers and facilitators common to different type of substances, we intend to inform the development of a behaviour change intervention applicable in high-income countries.

The synthesis of qualitative research was informed by meta-ethnography. Meta-ethnography is a methodology originally developed by Noblit and Hare with an interpretative approach [43]. This methodology is utilised to “put together” all the available research through the translation of qualitative studies into one another [43]. In order to do this, the researcher translates the studies into one another's terms, and into their own interpretation of the data and the world, which will result in a synthesis that is partially produced by the author [44]. To facilitate the reporting of this meta-ethnography, we followed The eMERGe reporting guidance [45] (see Supplementary Table 1). We chose meta-ethnography because of its potential to produce new interpretations, models or theory [46].

2. Methods

2.1. Search strategy

A comprehensive systematic search of the literature was performed for all qualitative research that explored women's facilitators and barriers to abstain from substance use during pregnancy. The databases searched were CINHAL, PsychINFO, Pubmed, SOCindex and Web of Science and the searches were conducted on the 28th and 29th of March 2019 with no restrictions on publication date. The search was updated on the 25th of November 2020 to identify new published articles relevant for our

synthesis. Further, the reference list of each included study was hand-searched for additional studies.

The protocol for this meta-synthesis was registered on Prospero (no. CRD42019120069). Originally this meta-synthesis had the objective to provide insights into different modifiable risk factors for stillbirth. However, due to the high volume and complexity of the qualitative research on antenatal behaviour practices, this meta-synthesis differs from the original protocol in that it focuses specifically on substance use during pregnancy rather than substance use, attendance at antenatal care and weight management as previously planned. Findings in relation to the other two modifiable risk factors will be published elsewhere.

Search terms were selected based on a preliminary scan of the relevant literature. The search terms used were facilitators, barriers, promoter, benefit, attitude, opportunity, determinant, promotion, intention, education, initiative, prevention, pregnancy,

smoking, smoking cessation, nicotine, alcohol, alcohol abuse, alcohol drinking, drug*, drug abuse, illicit drugs, oral drugs, intravenous drugs (see example of search in Supplementary file 1).

2.2. Study selection

Three members of the research team (SM, LL, TES) independently reviewed the titles and abstracts of the studies resulting from the database search. Additionally, two authors independently (SM, TES) conducted the full text screening of the eligible studies.

Studies were included for further review if (1) they used a qualitative or mixed methods design, as long as they included primary qualitative data, (2) they were written in English, (3) the participants were women interviewed when pregnant or up to 12 months post-partum as long as the data referred to their experiences during their pregnancy, (4) they were conducted in

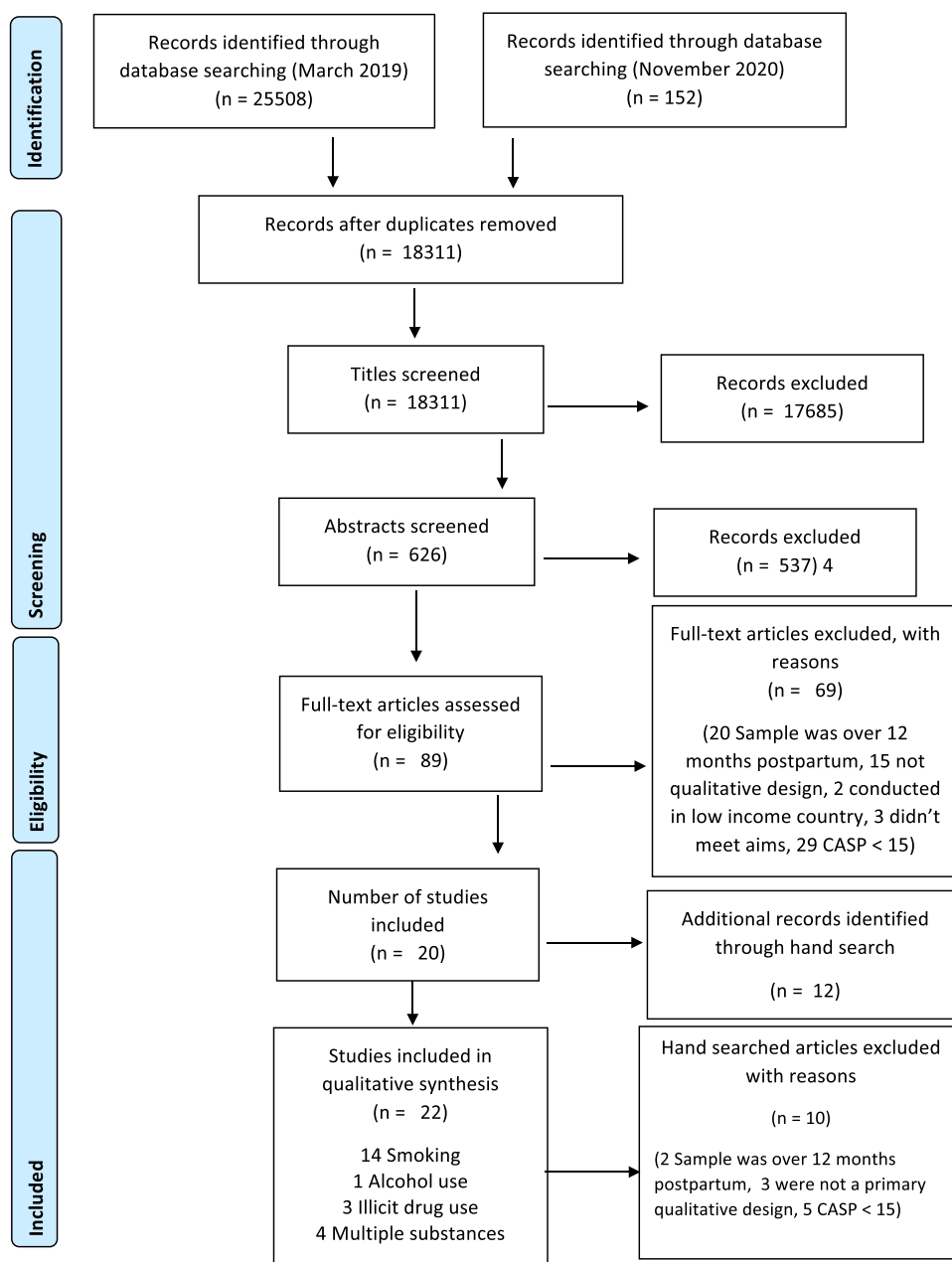


Fig. 1. PRISMA flow diagram showing the process of inclusion of studies. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097.

high income countries, and (5) included extractable data about facilitators and barriers to remain abstinent from substance abuse during pregnancy.

Studies were excluded if they did not include any qualitative data or if they were not original research. Studies that included different types of participants (e.g.: healthcare professionals and pregnant women, partners and pregnant women) were only included if the data extracted from the pregnant women was differentiated from the rest. In this meta-synthesis, we included studies that explored the views of women who were current substance users during their pregnancies and women who made the choice to remain abstinent during their pregnancy.

2.3. Data extraction

2.3.1. Study characteristics

A data extraction sheet was used to extract the characteristics of the studies by one author (TES). The following data were extracted from each study: country of publication, year of publication, aims, design, data collection method, sampling or recruitment strategy, consent process, number of participants, age of participants, pregnancy status, timing of data collection and method of data analysis.

2.3.2. Quality assessment

The *Critical Appraisal Skills Program (CASP)* for qualitative studies was used independently by two authors (TES, SM) to assess the quality of the studies. Previous research in the area of quality appraisal has concluded that there is a correlation between the quality of reporting of a study and its value as a source for the final synthesis, and therefore it is appropriate to exclude inadequately reported studies [47]. As a result, it was decided that only the studies with the highest quality (CASP \geq 15) would be part of the synthesis.

To assess our individual review findings, we used the GRADE-CERQual approach. This approach facilitates assessment of how much confidence can be placed on individual review findings from a synthesis of qualitative research [48].

2.3.3. Synthesis informed by meta-ethnography

Noblit and Hare (1988) [43] proposed a series of phases that overlap and repeat along with the conduction of the synthesis (see Supplementary Table 2).

Phase 1 and 2 – Selecting meta-ethnography and deciding what is relevant

The first two phases of meta-ethnography involve identifying a research gap which has the potential to be filled by meta-ethnography, explaining the rationale for using meta-ethnography and stating its purpose and focus, which we have done in the sections above. Phase 2 was completed by conducting a systematic search of the databases as outlined above, and importing the resulting studies into NVivo12 for analysis (see Fig. 1).

Phase 3 – Reading the studies

During Phase 3, the papers were read in depth several times and the characteristics and details of the papers were extracted and tabulated into the data extraction sheet (Supplementary Table 3). In this phase, each paper was read carefully and notes were used to identify the data that had to be extracted.

Phase 4 – Determining how the studies are related

Phase 4 involved the line-by-line coding of each selected study by one author (TES) using NVivo12 in order to identify common metaphors and concepts, consulting with the rest of the team when in doubt. We refined the codes in our list and created new ones as the coding progressed in each new study. Every sentence of the studies had to be coded at least once. A second author (SM) coded a sample of the papers to facilitate reliability and validity in

the coding process. Both first and second order constructs were extracted for analysis. We utilised second-order constructs to complement the primary data, which offered additional insights, context and explanations. Most of the studies had poor reflexive accounts, which hindered our assessment of the author's background influence over their interpretations. The key concepts explored and compared in the analysis were related to factors that either facilitated or hindered access to antenatal care for pregnant women in high-income countries.

Once the initial coding was completed, we examined the text added to each code for consistency of interpretation and additional coding was performed when necessary. We obtained a list of concepts that were grouped into themes and categories using thematic analysis.

We used tables to display the concepts and themes across all studies, classifying them depending on the substance they were exploring, this helped us see which concepts and themes juxtaposed across the different studies and substances explored (see Supplementary Tables 4a and 4b). Classifying the studies based on the concepts and themes and grouping them by substance helped us understand how the studies were related and in which aspects they were different. Then concept maps were used to establish and discuss the influences of each concept over the other. After this phase, it was understood that most studies related reciprocally, except those that explore different aspects of the topic.

Phase 5 – Translating studies into one another

Phase 5 involved translating the studies into one another. In this phase, the themes and concepts were further refined to ensure that the themes reflected the meaning of each individual study. The initial codes and themes were examined and combined thematically when describing similar findings.

The influence of each study over each concept obtained is documented using references and quotes. Quotes were obtained from primary study participants and by primary author's explanations and interpretations. Since the context of the studies were very similar, the studies were organised in sub-groups depending on the substance they were exploring (either alcohol, smoking or illicit drug use, which included Cannabis). In our study, similar contexts are beneficial as they allow us to identify specific facilitators and barriers. This would then better inform the development of a context-specific intervention.

In this article we are presenting first, second and third level interpretations, based on the women's experiences.

Phase 6 – Synthesizing translations

The result of the translated concepts, their relationships and the primary data were used to create a textual line of argument, which is presented here. Three authors were involved in the synthesis (TES, KMS, SM) and the additional authors provided feedback and insights when necessary (KOD, MB, LL). The authors are from different disciplinary backgrounds including psychology, sociology, medicine, public health, epidemiology and behavioural science, which promoted discussion of potential different interpretations.

Phase 7 – Expressing the synthesis

The findings of this meta-ethnography are presented in this article, additionally, a summarised version of the findings can be found in our CerQual assessment and summary tables (see Supplementary Tables 6 and Table 4a and 4b).

3. Results

3.1. Search outcome

Fig. 1 shows the process of inclusion of studies. The first database search was conducted in March 2019, and identified 25,508 studies. Of these, 18,159 remained after duplicate removal.

After screening for titles and abstracts, 85 studies remained potentially eligible for full text review. Following full text screening of the remaining 85 studies, 18 studies met criteria for inclusion in the meta-synthesis. Twelve more studies were examined for potential inclusion after hand-searching the reference list of the included studies, and 2 additional studies were included. The search conducted in November 2020 identified 152 potential studies. Four studies remained potentially eligible after screening for title and abstract, of those, two studies were included in our synthesis. The final number of studies included for synthesis was 22.

Several facilitators and barriers were identified during our analysis that have an influence on women's prenatal health behaviours. We classified these factors as internal factors or external factors, with internal factors being those that the woman might have some degree of control over and relate to her own beliefs, knowledge and intrinsic motivation to decide whether to use or not substances during their pregnancy. External factors are those which will have an influence on the woman's behaviour but are elements over which women have very limited control and relate mostly to their social environment or the healthcare system.

3.2. Study characteristics

The characteristics of the studies included are shown in Supplementary Table 3. Of the 22 studies included for analysis, 14 focused on smoking, 1 on alcohol, 3 on illicit drugs and 4 on different multiple substances. Six were conducted in the UK, 3 in the USA, 3 in Australia, 1 in Canada, 1 in Sweden, 1 in Finland and 1 in New Zealand. The years of publication ranged from 1998 to 2020.

Twenty-one of the studies were qualitative and one mixed-methods. The studies used different data collection methods; nineteen used semi-structured interviews, three used focus groups. The number of participants in the studies ranged from 6 to 53, with ages ranging from 15 to 49 years. Thirteen of the studies included pregnant women only, one included only postpartum women up to 12 months after birth and eight included both pregnant and postpartum women. Regarding the quality appraisals, most of studies performed poorly with regards to reflexivity and ethical considerations, and performed particularly well in the reporting of their aims, qualitative methodology, recruitment strategy and data collection methods justification (See Supplementary Table 5). Results from the GRADE-CERQual analysis are presented in Supplementary Table 6.

4. Synthesis

4.1. Internal factors

Theme 1: Perceived incentives

In this theme we identified internal factors reported by women that might increase or decrease their levels of motivation to use substances or remain abstinent. Women reported perceived psychological and social benefits from their substance use, and additionally, women expressed reasons why interrupting/ceasing their use would have negative consequences upon them. However, some other women were also able to identify benefits of abstaining from substance use.

Category 1.1: Perceived benefits obtained from substance use

Women reported several **reasons for continuing to use substances** during pregnancy. Lack of motivation to quit [28,30,32,49,50] and boredom [28,30,32,50] were two reasons commonly reported.

“So you're bored, what are you going to do? Sit down and smoke a cigarette.” [30]

“The part that wants to quit is smaller than the part that doesn't.” [30] [Smoking]

Furthermore, women reported obtaining benefits from the use of the substances that act as barrier to remain substance free. The most commonly reported benefit of substance abuse was that *“It makes me happy; it relaxes me”* [30]; hence, many reported that due to this *“total relaxation feeling”* [51] they used their habit as their main **coping strategy for stressful situations** [28[30,31,49–55]. For many women abstaining from the drug meant losing their only coping strategy for stress [28,30,49–53]. Taking the time to have a drink or smoke a cigarette gave them a sense of freedom and private time [31,52] whereby it was *“the only time I get a 5-minute break”* [28]. In other cases, women also spoke about how using their substance of choice has a positive effect on their mood [49,51], and the substances were perceived as source of enjoyment and socialisation [37,53,56]. In these cases, despite the fact that women might acknowledge the risks of the substance use, the benefits obtained outweighed the risks.

“Smoking and drinking were an important part of her social life, and although she always imagined she would quit when she became pregnant, she found she was unable to do so” [53]

“I felt like it was consistently helping me calm down and be able to function enough – well enough to parent my six-year-old as a single parent and, um, deal with that” [55] [Cannabis]

In the case of Cannabis in particular, women spoke about its therapeutic effects [55]. In one of the studies conducted in an American state where Cannabis use was legalised, women from different socioeconomic backgrounds used Cannabis to control their nausea, increase their appetite and manage stress as a *“more natural alternative than prescribed medications”* [55].

“It helps me feel hungry and it takes away my nausea completely. And it helps with the pain, too. And not so much that it takes away all of my pain, but it helps me mentally manage by pain better.” [55]

In addition, some perceived **disadvantages of remaining abstinent** were identified, including fear of harming the baby due to the consequences of the abstinence [28–31,56,57]; for instance, having increased levels of psychological stress [29,30,50,53,58] which women perceived as more harmful for the baby than the substance use itself [29,50]. The withdrawal symptoms and cravings as a consequence of the addiction to the substance [30,35,57,59] that in some instances lead them to feelings of loss of control [49] were also a source of concern. Additionally, women were concerned about the effect of abstinence on their relationships [30,35,57,59], since using is a common habit within their partner and/or wider social circle, whereby reported that they *“feel left out of some situations with my friends”* [56]

“There was a couple of times I just tried stopping, just getting sick. I would get a day into the sickness and it would just get to the point where it's just . . . I'm running out the door [to get more drugs.]” [57]

Regarding smoking, women were concerned about gaining too much weight if they attempted quitting [56,58]. Since smoking was their main coping mechanisms for stress [30,53,56,58], women reported that they would probably resort to food as means of getting comfort when not being able to use cigarettes [53,58]. When speaking about illicit drug use, women were especially concerned about their mental health [35] and their perception that their life would feel dull without the effects of the drugs [35].

“I either eat or smoke . . . I make the choice, I don't want to get big, so I'll go smoke” [56].

Category 1.2: Perceived benefits obtained from substance abstinence

Within this sub-category, women spoke about **practical benefits** for their life, such as hygiene and money saving aspects [28,49,50]. But the main benefits identified by the women were related to their own and their baby's health [31,37,50,52–54,56]. Additionally, some emotional benefits for the women were also identified. Women felt a sense of relief from the guilt of using substances [37,52,53], and felt that they were giving a good example to their children by remaining substance free [56]. Furthermore, some women spoke about developing an increased perception of willpower and self-efficacy as consequence of their achievements during their process towards abstinence [28,37,53,60].

For some women, **being pregnant or having other children** was already motivation enough to attempt quitting, engage in harm reducing actions or to abstain from drugs completely [31,37,52,54]. Some women reported that “*No one is more special than my baby*” [53] adopting a moral responsibility towards prioritising their baby's wellbeing which facilitated that they remained substance free [31,32,37,51,53].

“There's a baby inside you. You know you've got to do it.” [52] [Smoking]

“My kid at 5 telling me that he doesn't want me to die, it was heartbreaking” [28] [Smoking]

“The only reason why I quit was because I was pregnant, so I mean, if I hadn't fallen pregnant, I'd probably still be smoking cigarettes now”

Another factor associated with the pregnancy that acted as a facilitator was the pregnancy-related sickness, women found that smoking or drinking alcohol during their pregnancy made them feel sick resulting in women decreasing their substance use [28,53,54,59].

“Look, I don't want to be like a reformed bitch of smoking, but the smoke is just making me sick.” [53]

Theme 2: Feelings of shame and guilt

In most of the studies, women referred to feelings of guilt and shame due to their substance use [28,31,49,53,56,58,61]. These negative feelings in combination with the external pressure from their social environment acted as barriers to abstaining from substance use for some women whereby “*you feel even worse and in the end it becomes too much*” [49] resulting in women's stress levels increasing which lead to increased use of the substance as a coping strategy [49,58].

I just can't stand it. Sometimes I'll even try to turn the guilt off, and it's like it's still in my head and, you know, what I'm doing and I don't know why, it's just so hard for me to quit. Oh, and the baby will kick when I'm smoking, it almost makes me like cry because it's just like, I shouldn't. [53] [Smoking]

4.2. External factors

Theme 3: Knowledge and information

Category 3.1: Knowledge about the risks of substance use

Many women discussed a lack of accurate knowledge about the risks women were taking when using substances during pregnancy. One factor that contributes to the generalised lack of accurate knowledge is the **use of anecdotal evidence as a source of information** and justification for substance use. Regardless of the substance, women often discussed their previous pregnancies or people they knew or heard of that had used substances during their pregnancy who had a healthy baby [28,30,31,35,37,49,

51–53,57,58]. Generalising these individual cases might be contributing to the creation of misconceptions about the risks. Furthermore, using these counter examples as justification might also be used as a coping mechanism to reduce the guilt associated with their substance abuse.

“I drank a little bit with my first child and I carried on doing that with my second and third pregnancies. My first child is absolutely fine.” [51] [Alcohol]

“So far from what I've seen, any girl that I know that's done dope throughout their pregnancy, their kids are really overachievers. Which, I'm not trying to say, ‘use meth, it'll make your kids smart.’ I'm just saying that the ones that I do know, there's nothing wrong with their kids.” [57] [Illicit drugs]

Women reported **misconceptions about the risks of substance use**, which were likely a consequence of using unreliable sources to obtain information in combination with the anecdotal evidence explained above. For instance, only heavy use was perceived as dangerous by many women [31,35,51–55,57–59] and hence “*If you drink in moderation and you're sensible, then I don't think it affects the fetus*” [51]. The distinction between heavy and light use was made by the women in a subjective way, and in many cases, it was not based on medical evidence. For example, light alcohol use was defined by women as “*one sip of wine*” [31], “*one or two [drinks]*” [31], “*drink in moderation*” [51]; whereas women defined light smoking as “*four a day*” [58], “*an odd fag [cigarette] now and then*” [52], “*under ten cigarettes a day*” [53] or women considered illicit drug use safe when used “*in low and steady doses*” [35,57]. Further, certain substances were seen as more dangerous than others [30,31,35,53,55,58] “*alcohol was really bad, but there was no proof that meth did anything to the babies*” [57], and some women thought that the consequences of quitting could be worse than the consequences of using [30,35,53,57]. Some women also believed that the properties of the substance might benefit the baby [31,51,57], with a women reporting that “*babies that have been drug exposed may be more gifted, more creative, and more beautiful.*” [57]. Other women thought that the risks are exaggerated [28,30,35,49,51, 53,57,58,61], believing that the consequences of substance use on the fetus are “*things that are fixable*” [28] once the baby is born [28,30,57]. These misconceptions can act as barriers as women rationalise their substance use and decrease the feelings of guilt that women report feeling.

“I don't want that to sound nasty, but like having a small baby, the baby will grow, he can put on weight. . . and doctors are amazing now like. . . there's more chance of the baby developing a cleft lip as well, that could be fixed with surgery.” [Smoking] [28]

Another barrier to remaining abstinent is that some women believe “*nothing will happen to you*” [58] and “*nothing happens to the baby either*” [58] and so they do not feel susceptible to the potential harms of the substances [28,30,49,51–53,57,58]. In these cases, despite having some knowledge or awareness of the risks, women share the belief that this cannot happen to them, that “*it only happens to other people*”.

On the other hand, having more accurate knowledge about the risks of substance use acted as a facilitator to prevent substance use during pregnancy [28,30–32,35,37,49,51–54,56,57]. In the case of alcohol, for instance, since the information about its risks can be contradictory and confusing, women tended to “*go for the safety aspect, so because I'm not 100% sure, I just completely abstain to be on the safe side.* [Alcohol]” [51].

In the case of smoking, besides being aware of the risks of the smoking itself [30,32,53,56,58], having knowledge about the risks of passive smoking [28,58] and the influence of smoking on breastmilk [56] also acted as facilitators.

“It gets not only into your lungs, but it gets into your bloodstream and everything, so why wouldn't it get into your milk and go to the baby?” [56] [Smoking]

Despite the fact that many women resort to counter examples and misinformation about the risks to rationalise their use and reduce their feelings of guilt, most of them are aware that there are certain risks associated to their behaviour [28,30–32,35,37,49,51,53–57,59]. This awareness led some women in these studies to **take action in order to minimise the harms produced by their use** [53,54,56–58]. In some instances, these changes were in line with common recommendations, whereas with others they were in response to their own perception of what was best for the baby.

The most commonly reported strategy to reduce harm was trying to abstain or cutting down the substance use [28,31,50,53,56–58]. Cutting down to levels considered “*not that much*.” [58] was perceived as a positive solution to balance the baby's needs with their own needs, and it was advised by healthcare professionals when unable to abstain completely [53,58]. Women also tried to compensate with other health behaviours [31,50,53,56–58] such as “*eating more frequently*” [57] and “*sleep every night*” [57], and keeping themselves busy and distracted whereby “*instead of smoking, doing the kids' sandwiches*” [54] or doing exercise to release stress [54]. Other women limited relationships with other users [57]. Women also reported changing their habit to what they considered safer [28,53,57], for example switching substance [57] or type of administration [57]. Although not always adaptive, these behaviours show that women have some motivation to change their habits and therefore considered them facilitators.

“We posted a big sign on the front door saying, ‘No Drugs.’” [57], “I was just like, well, ok, in the morning I can just drink coffee instead [of using methamphetamine].” When this didn't work, she tried switching to drinking alcohol, “I will just replace that [methamphetamine] with X amount, with alcohol” [57]

Category 3.2: Sources and quality of information

On several occasions, women reported a **lack of sources of information** regarding the risks of the substance they were using [28,31,35,51,55–57,59]. There was a perceived lack of evidence about the risks reported by women [35,55,57] “*I've actually heard they don't exactly know what is safe and what isn't. Because they don't know they say not to do it [Alcohol]*” [31], and in many cases, women spoke about not having specific information [28,56] about “*what damage does [Smoking] actually do to the placenta, you know, proper sort of medical facts*” [33].

“If I was given more information, you know, per scientific research studies, I could maybe make a more informed decision” [55] [Cannabis]

Another reported issue that acts as barrier is the **poor communication between healthcare professionals** and women about substance use. Women reported only being asked about their substance use at their booking visit “*there was no other conversation about it*” [31] or if there was discussion it was on very limited occasions [28,31,32,55,56]. The discussions about their substance use were very superficial and generalised, and lacked practical advice [28,30,53], leaving women with poor understanding of the risks [28,56,58].

“My doctor just tells me that it's really important for me to quit. Well, I know that already, and I want to quit too. If it were so easy, I would have done it already. So when he says that to me, I just say, “Okay,” and that's the end of the conversation” [53] [Smoking]

Further, on several occasions women spoke about receiving **conflicting information** from different sources [29,31–33,51,55,59], including amongst different healthcare professionals [28–30,32,33,50,53,55,56], and also, there were occasions in which family or friends of the woman would act as source of information [35,61].

“So like my GP I didn't really get a definitive answer . . . Whereas when I went to my midwife, for my antenatal appointment that was clearly communicated from day one . . .” [31].

“My doctor, he doesn't like that I use marijuana at all. [. . .] And once I was pregnant, he's like, ‘You've got to stop.’ And I did stop when we talked about it. But then when I told him my OB's decision to let me linger a bit, at least until I'm like 20 weeks or so to see if the morning sickness goes away [. . .] He doesn't like it, but my OB doctor totally understands.” [55]

Theme 4: Experiences within healthcare system

Category 4.1: Relationship with healthcare professionals

Women expressed feeling judged and stigmatised for their substance use during their **antenatal care** [29,30,32,35,52,61]. Women spoke about not being treated like ‘normal’-expectant mothers due to their substance use [61].

“You just knew that you were not going to be treated equally and like other pregnant women and accepted for who you were. I mean after all I was at the clinic because of drug problems, and that was never forgotten [by the staff]”. [61] [Illicit drugs]

Women also reported a **lack of encouragement or insensitive attitudes** from healthcare professionals during antenatal care [30,50,58,61], which together with a perceived prioritising of the baby's needs over their own needs [61], became a barrier to motivate women.

“. . . Never a hint of praise for coping the best you can. No-one ever asked me a really personal question that might have a happy answer” [61] [Illicit drug use]

When discussing their substance use, some women explained that they found that healthcare professionals adopted an **authoritarian or coercive communication style** [28,32,49,50,61]. As with the general negative consequences of the social pressure, women perceived this communication style like an additional stressor or a challenging attitude.

“They [midwives] just keep telling me to stop. . . it winds me up a little and makes me worse [with smoking].” [54]

Women also reported some issues with regards to the staff working in the cessation treatment centres for illicit drug users similar to those encountered with the antenatal care staff. Women felt judged and stigmatised, and perceived that staff were biased towards the patients [61] perceiving some of them as too challenging or hopeless [61].

Hence, according to these women's experiences, it seems that healthcare professionals' attitudes and behaviours might be influencing the women's process towards abstinence by potentially preventing care-seeking behaviours or adherence to treatment, increasing stress and consequently use of the substance as coping strategy and missing opportunities to educate and inform women accurately about the risks of their substance use.

In other cases, women also spoke about finding **supportive and encouraging healthcare professionals** that facilitated their quitting process [28,35,53,54] who were “*like a nagging mom, but in a good way*” [53]. Further, healthcare professionals with an empathetic and non-judgemental attitude were valued by women as well [30,32,33,49,53,54,56,58,61].

“When I walk in her room we have a good laugh and a good giggle and we have a good chat, she isn't one of these that just gets

straight down to business and lets you blow in the meter and sends you on your way and just asks you questions and questions and questions, she makes sure that you're alright in yourself." [Smoking] [54]

Category 4.2: Practical limitations of drug cessation treatment centres

Women using illicit drugs also reported several limitations within the **cessation treatment centres** that acted as barriers for them to engage in care. Women reported having to choose only one child to take with them into the residential treatment center [34], being rejected for being pregnant [34], not being able to meet pre-admission requirements or finding the referral system too complex [28,29,34] which led them to perceive these centres as unhelpful and an additional source of stress [28,34].

"There was an opening for here [the treatment program]. But the only hardest part was I had to choose one kid . . . (crying) So . . . they (child welfare) came and got my ten-month-old, and my two-year old came here . . . It's not fair . . . (crying) Because he's only a baby, he didn't deserve all this. I had to do it by myself . . . just what I thought would be best." [34] [Illicit drugs]

Theme 5: Influence of social environment

Category 5.1: Social disapproval

The **social disapproval associated with substance use during pregnancy was experienced as having disadvantages** [28,29,31,32,50,54,55,59]. Women spoke about feeling questioned, judged and labelled as "just a coke head with a 12-year-drug habit" [61] by other people [28,31,32,35,61] which led them to think that they were being perceived as bad mothers. The external social pressure to which women were exposed from their family members, partners, healthcare professionals, etc. acted as barrier since it increased their levels of stress [28,30,32,49,50] and sometimes was perceived as a challenge to their individuality [59]. Hence, due to the negative feelings produced by external pressure in addition to their own feeling of guilt led women to hide when using substances or avoid disclosure [29,31,34,52,53,58,59,61,62].

"in the end if my partner said anything I kind of just did the opposite just to you know prove a point . . . this is my baby and my pregnancy" [59] [Alcohol]

"I did smoke with them but it was in my own house, I never walked around out and about with one, it's not the best look" [59]

However, some women find this perceived social disapproval as a motivator for change [31,56]. Hence, social disapproval also has some benefits. In these cases, women wanted to be perceived as good mothers which acted as a facilitator to reduce or eliminate substance use. In other cases, women perceived their substance use as "a family decision; it's not just about me" [31].

"Several women felt that the decision not to drink was a family decision as it would have effects on the baby, and that their partner had input on many of the health decisions made during pregnancy." [31]

However, after doing our CerQual analysis, we concluded that this finding – perceiving social disapproval as a motivation to change- has serious limitations and hence the level of confidence assigned to it is low. This is because only two studies with moderate methodological limitations support this finding.

Category 5.2: Influence of type of support from close environment

A **lack of support in close environments**, which include people that the woman shares a house with, their family, partner, friends and work environment, has been reported in several occasions as an external barrier to remain substance free. Women reported not having their partners support to remain abstinent as a

barrier [28,29,31,35,50,52]. The fact that their partner used the same substance and "was smoking around me all the time" [50] was reported as a barrier by women [28,29,31,35,53,54]. Further, women also spoke about perceiving inconsistent attitudes towards substance use from their partners that led to frustration [53]. Specifically in the case of smoking, women spoke about their partners not maintaining their habit changes over time, feeling pressured and guilty by their partners to quit smoking while their partners themselves were still smoking [28,50,53] and being encouraged by their partner to smoke lightly in times of stress [50,53].

"It made it hard (staying smoke-free) because my husband had not tried to give up and . . . it was constantly in my face and he would say, 'Come on outside and have a smoke with me you won't be so stressed'. I gave in. It was my own fault for giving in." [50]

For some women, substance use is a normalised event in their family and they have always been exposed to it, especially in the case of smoking [32,53,54,56,59]. Family members showing resistance to change their own smoking habits also act as barrier [58]. Some women need to share their homes with extended family and are exposed to second-hand smoking which makes them feel frustrated [53,54,56,58,60], but they feel powerless to enforce any changes.

"My family smokes, my friends smoke . . . everyone's smoking . . . It's gonna be a challenge" [53]

"Well quite a few of my family smoke, so, I mean I'd say that tempts me to smoke when they're around and stuff ;" [54]

On the contrary, a **supportive close environment** can also facilitate women's attempts to remain substance free. Women that reported having supportive partners that are "probably drinking less . . . because he's not drinking" [31] or changed their habits in some ways to avoid exposing the women to the substance were very helpful in their own quitting process [28,30,31,50,54]. Further, environments that discourage substance use and limit people's access to it as facilitators [28,53,54].

"I asked him to buy cigarettes for me once because I was really losing my mind and he would not do it" [31].

"Because I'm doing an 8-h shift on my own, so there's like 9 hours where I'm not smoking" [28]

Category 5.3: Socioeconomic factors

Regarding the wider context, there were some **socioeconomic factors** that act as barrier to remain substance free [32,34,35,53,60,61]. Some women found that seeking care to reduce their substance use was not their priority, since they have other more immediate needs to attend to [28,29,50]. For instance, women reported transportation issues [28,29], housing and food insecurity [29], financial issues [28] and domestic violence [34] as barriers. These women experienced chronic high levels of stress and resort to their substance use as source of comfort [53].

One of the commonly reported barriers associated specifically with the use of illegal substances was the concern that women "could have been arrested" [34] due to the potential legal consequences of their use. Women actively avoided attending antenatal care or disclosing their substance use due to fear of losing custody of their babies [34,35,37,55,57] or being legally prosecuted [34]. Even in the case where Cannabis use was legalised, women were still confused and concerned about potential legal consequences due to their use during pregnancy [55].

"If you have another [drug-exposed] child within a three-year period, even if you're staying clean and sober, your child will be taken from you . . . I was really scared of that . . . that's what kept me from going to prenatal care." [34]

“And I was like, ‘Is that like legal? Can you smoke while you’re pregnant?’ And she said that I can’t get in trouble for it, but I still worry a little about it. She said, ‘Just be aware that if you use any for labor or anything like that, do not let the nurses know at the hospital because they will report you to CPS.’ She said, ‘I will not. I would not do that.’ . . .] She said, ‘Just be aware the nurses at the hospital have a different view.’ ” [55] [Cannabis]

5. Discussion

This meta-synthesis identified factors that can act as facilitators and barriers influencing whether women would try to abstain from substance use (either smoking, alcohol or illicit drug use) during their pregnancy. Importantly, despite the fact that the facilitators and barriers identified in this study have been divided into different categories and themes, these factors can co-occur and must be considered together to be able to understand the complexity of substance use during pregnancy. Women reported perceived psychological and social incentives associated with substance abuse, and for many women, their substance use was their only coping mechanism for stress. However, benefits of remaining abstinent such as improved hygiene and health and money saving were also reported as facilitators. Another barrier identified was related to the shame and guilt that some women feel due to their substance abuse which created negative feelings and increased levels of stress. Poor information, communication and knowledge about the risks together with lack of discussion with the healthcare professionals and the conflicting information available acted as a barrier which made some women resort to anecdotal evidence or unfounded beliefs to justify their substance use. On the contrary, women with some awareness of the risks tended to adopt cautious attitudes or engage in harm-reducing strategies. Women also spoke about the influence of the type of support they received from healthcare professionals. Being exposed to social disapproval made them feel questioned and labelled. However, for other women this social pressure acted as motivation for change. Non-supportive, stigmatising and judgemental healthcare professionals acted as a barrier to remain abstinent, whereas encouraging and empathetic healthcare professionals were highly valued. Further, the social environment of a woman can have a negative influence, including lack of support, and additional socioeconomic factors such as housing and food insecurities, unstable jobs and financial issues were identified as external barriers.

The results of the study show that some women were incentivised by the effects of substance use to continue using. Women utilised substance use as a coping strategy with psychological and social benefits such as stress reduction, relaxation feelings and mood improvement. These results are in concordance with previous studies that have established stress as a risk factor for substance use [63–65]. Consequently, the balance of perceived benefits versus potential health, psychological and social risks that substance use has for these women will determine their attitudes towards it [66]. According to the Theory of Planned Behaviour, behavioural intentions are a result of attitudes and subjective norms [67]. This model also adds the concept of perceived behavioural control, which relates to individuals’ perceived difficulty to perform a behaviour [67]. Behavioural intentions and perceived behavioural control are considered main determinants of behaviour change, which, according to the Theory of Planned Behaviour, means that this change can only happen when there is a change in the beliefs that influence the intentions and the perceived behaviour control [66,67]. Our results show that in some cases the benefits that these women obtained from their substance use were perceived to outweigh the perceived risks,

which might lead them to have a positive attitude towards engaging in substance use. However, the results also demonstrate that some women lack accurate knowledge about the risks, which might mean that this process of deliberating benefits and disadvantages might be biased towards the benefits. Previous research has demonstrated that deficits in health literacy can be translated into a poorer health status as it acts as a barrier to healthcare and can also impact people’s decision-making [68]. Additionally, some women spoke about feeling a loss of control when having cravings and perceiving themselves as incapable of remaining substance free. These feelings of low self-efficacy and lack of control over the substance use might influence the women’s perceived behavioural control in a negative way. This is in concordance with previous studies looking at perceived self-efficacy and behaviour change in different populations, where the authors concluded that the lower the perceived self-efficacy the minimal will be the behaviour change [69–71].

Stress also seemed to be related to substance use in our results. Exposure to stress involves changes affecting nearly every system of the body, influencing how people feel and behave [72]. Lazarus and Folman’s Transactional Theory of Stress and Coping explains that, when dealing with a given situation, individuals first assess whether a specific/individual transaction is positive, neutral or stressful [73,74] depending on the consequences it can have on their well-being. When a transaction is considered stressful, the individual will have to evaluate their coping resources (self-efficacy), the situation variables (level of control), and their coping styles (coping mechanisms used or learnt in previous similar situations) [73], and this coping styles can be directed at tackling the stressor (problem focused) or to regulate the emotion caused by the stressor (emotion-focused coping) [73]. In the context of pregnancy, coping efforts might influence birth outcomes since they can serve as a resource to prevent prenatal stress exposure to the infant [75]. Positive reframing, acceptance and seeking emotional support are coping strategies that have been seen to have beneficial effects on antenatal anxiety, worries and depression [76]. However, results from our study show that the substance use acted as their main coping mechanism for many women. Hence, in the case of these women, not only is the exposure to stress detrimental to the infant, but also the coping mechanism. Since this strategy does not directly manage the stressor, we could classify substance use as an emotion-focused coping strategy within the transactional model [77]. Although emotion-focused coping strategies can be adaptive when the stressful situations provoke intense emotional reactions or distress, the stressor is perceived as uncontrollable or when the person does not have enough resources to use a problem-focused strategy, they have been proven to be ineffective long term [78].

Hamilton and Lobel conducted a study with the aim of determining how women cope with stress across pregnancy [79]. The authors used the Revised Prenatal Coping Inventory (NuPCI factors) to explore the different coping strategies potentially used by women and concluded that higher state anxiety and pregnancy specific distress were the strongest predictors of use of avoidance as coping strategy throughout the pregnancy [79]. These results are in concordance with the relationship found between high levels of stress and use of substance in our study. Avoiding coping style and behaviours during pregnancy such as substance use have also been associated with a wide range of adverse mental health outcomes such as increased distress, higher depressive mood, increased anxiety, higher perceived stress and greater child abuse potential [75,79–81]. Hence, the circle between high levels of stress and substance use might be a partial explanation as to why women maintain their substance use during pregnancy. Further, some women in our study were aware that stress can be detrimental for their unborn child, and considered that the

increased stress that abstinence brought to them would be more detrimental than the substance use itself and hence the substance abuse would have a protective effect for their babies.

Women spoke about feelings of guilt and shame due to their substance use. These feelings could be a consequence of the cognitive dissonance created by their substance use and their awareness of the risks of their substance use. According to the theory of cognitive dissonance, this occurs when a person holds two inconsistent thoughts, in the case of the women in our study, the substance use and the awareness of the risks of these substances [82]. The existence of cognitive dissonance can be psychologically and physically uncomfortable [82], which might explain the feelings of guilt referred by the women. When cognitive dissonance is present, the person might try to reduce it using different strategies: by avoiding situations or information (which in our study translate as using unreliable sources of information such as anecdotal evidence), adding additional thoughts to rationalise the inconsistency (which we observed as accepting unfounded facts as true), or trivialising the inconsistency (like using unrealistic optimism expressed by some women in our analysis) [82]. Behaviour change is needed to reduce cognitive dissonance. Although information and education is not enough to change behaviour, it can be a first step [83]. This generalised lack of knowledge about the risks of substance use during pregnancy might partially be a consequence of the reported lack of accessibility to sources of information, the limited discussion with healthcare professional as well as the conflicting messages from different sources. It is crucial to make sure women are making informed decisions based on current evidence instead of resorting to non-adaptative strategies to reduce their cognitive dissonance.

An additional issue identified within this study was related to the level of stigmatisation that women were subjected to, especially during their pregnancies. Previous research in the field of substance use has shown that stigmatising attitudes towards drug users are common, not only amongst the general public but also amongst non-specialised healthcare professionals [84]. This leads people with substance abuse problems to have ambivalent attitudes towards seeking treatment due to the negative connotations associated with it which they would not identify themselves [85]. Additionally, the fear of reprimands or legal consequences also acted as a barrier for care seeking and disclosure of their substance use as shown in our results, even in the cases where the substance use was legalised. Relatedly, our results show that it is crucial for women using substances to find a non-judgemental and non-authoritarian space within their antenatal care in order to feel safe to disclose their use and seek additional care when necessary.

Our results also show that substance use is a common event for many women in their families or close social circle, which not only acts as a social facilitator for substance use but also might have led some women to normalise the use of substances as a coping strategy for stress through a process of observational learning and imitation [86]. Further, the perceived lack of alternatives and lack of control over their environment, might contribute to this phenomenon. These results can be explained by the Social Learning Theory that postulates that adults who present themselves as role models while being involved in addictions, will have a strong effect on reinforcing other people's addictive behaviours, especially if there are social reinforcements associated to this behaviour [87,88]. Women in our study struggled more to remain abstinent when their partners or close environment continued to use the substance in their presence. Stimuli and environmental factors can act as cues for substance use through a process of classical conditioning [87]. Hence, it would be beneficial for the women to involve their partner's or closest social influences into

the abstinence process in order to encourage and promote healthier pregnancy habits.

The social environment to which a woman is exposed will have an influence over their substance use habit. The Social Determinants of Health framework developed by Dahlgren and Whitehead [89] could be used to explain this influence. According to this framework, social aspects such as the conditions under which a person grows up, the availability of social support, community network, access to education, housing, employment, health services and water and food supplies will have an impact on the health outcomes of an individual [90–94]. Our results show that certain factors such as housing and food insecurity, unstable jobs, financial issues and domestic violence as barriers to seek care for their substance use. Those factors will have an influence on the women's ability to remain substance free, and hence, interventions targeting the different levels need to be developed to make sure that the issue is addressed as a whole [93,95].

The National Institute for Health and Care Excellence (NICE) guideline for substance use during pregnancy recommends healthcare professionals refer women who misuse substances to appropriate substance misuse programmes as soon as they disclose the pregnancy [96]. Additional relevant support services should also be recommended and encouraged based on the woman's individual needs [96], this is very relevant as women in the studies explored reported a need for more individualised care. Further, the NICE guidelines also recommend offering women with information about the potential effects of substance use on her baby and what to expect when the baby is born, which matches the need reported in our study for further information and discussion with healthcare professionals. These guidelines also acknowledge the importance of the healthcare professional's attitudes and how these can prevent women from engaging with the services provided [96] which we also identified as a barrier for care seeking and disclosure.

According to Flenady et al., a large proportion of stillbirths occurring in high-income countries are avoidable [97]. Increased clinical and community awareness of the modifiable risk factors associated with stillbirth might improve prevention efforts and reduce stillbirth rates, and we believe that the findings of this study provide additional detail and context that could be valuable for this purpose.

There are some limitations to our study. Firstly, we used a limited number of databases to conduct our systematic review. These databases were selected based on similar studies in the area, previous experience and knowledge about the databases scope. Secondly, some studies were excluded based on quality assessment. This decision was made to enable the findings of our studies to be of high quality, however, excluding studies based on quality appraisals might result in a loss of relevant input. Thirdly, the findings obtained from this study are based on women's experiences and interpretations and should not be understood as facts. Additionally, our findings are based on the secondary analysis of the primary data, collected and analysed by the studies' primary authors. Although the findings across the studies were consistent and we conducted a CerQual assessment to evaluate the confidence of our findings, it is important to acknowledge this potential influence over our findings. Finally, the publication dates of studies included in our analysis range from 1997 to 2020. There is a possibility that findings may have been influenced by variations in antenatal care over time. However, similar themes were identified in studies regardless of time of publication.

In conclusion, interventions need to be designed at different levels to address the issue of women using substances during pregnancy. Factors such as misinformation and lack of knowledge about the risks of substance use should be targeted with the women, this could contribute to the creation of more accurate

balance of the real risks and perceived benefits of substance use during pregnancy. Hence, women need to be provided with accurate and accessible sources of information, and discussion with healthcare professionals needs to be encouraged. Additionally, women under these circumstances would benefit from interventions targeted at developing new coping mechanisms for stressful situations.

However, there are external factors that also need to be targeted in order to minimise barriers for these women. Non-specialised healthcare professionals should be educated on the complexities of substance use to encourage non-judgemental and sensitive attitudes. The social circle of the woman must also be addressed, involving the women's partners, family and friends within the quitting process might be helpful. Moreover, especial considerations need to be taken into account with women in vulnerable socioeconomic situations.

The facilitators and barriers identified in this study can serve to inform the development of a behaviour change intervention to tackle this issue and help prevention efforts towards reducing the risk of stillbirth.

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Conflict of interests

The authors would like to report no potential conflict of interests.

Ethical statement

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CRedit authorship contribution statement

Tamara Escañuela Sánchez: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Karen Matvienko-Sikar:** Investigation, Supervision, Writing - review & editing. **Laura Linehan:** Investigation, Writing - review & editing. **Keelin O'Donoghue:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **Molly Byrne:** Conceptualization, Supervision, Writing - review & editing. **Sarah Meaney:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.wombi.2021.04.010>.

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