

Summary:

- There is insufficient evidence that maternal cannabis use causes low birth weight or long-term adverse developmental outcomes.
- No negative effects are attributable to cannabis exposure when tobacco and alcohol use are properly accounted for.
- Designating cannabis and THC as reproductive toxins under Proposition 65 would misdirect public health and harm reduction efforts away from known teratogens, like alcohol and tobacco.
- Although cannabinoids are not intrinsically toxic, they may amplify the toxic effects of alcohol, nicotine, and other teratogens. Thus, public health messages should be tailored towards pregnant women using multiple substances.

Introduction

Labeling cannabis, cannabis extracts, cannabis smoke, or THC as reproductive toxins is not justifiable from high-quality scientific evidence.

The concerns surrounding cannabis in pregnancy have far outpaced scientific data showing ill effects. These fears are engendered by poorly designed studies that fail to account for exposure to well-established teratogens, like tobacco and alcohol, as well as confirmation bias and misunderstandings of statistics.

In nearly every primary study that argues cannabis use during pregnancy is harmful, the authors admit that results are confounded by other drug use. But rather than designing better studies, these repetitious faults are allowed to accumulate, creating a body of research that *feels* like it demonstrates that cannabis is dangerous in pregnancy. In fact, proper analysis of the currently published data indicates the opposite.

The consensus of meta-analyses actually provides some (albeit weak) evidence that cannabis does not lead to negative outcomes in pregnancy, as highlighted in a 2016 publication from the *American College of Obstetricians and Gynecologists*: “Although these data do not imply that marijuana use during pregnancy should be encouraged or condoned, the lack of a significant association with adverse neonatal outcomes suggests that attention should be focused on aiding pregnant women with cessation of substances known to have adverse effects on the pregnancy such as tobacco,” not cannabis.¹

Why are only meta-analyses considered as “high-quality” evidence?

This public comment only considers meta-analyses, a type of study that attempts to draw firm conclusions from the weight of published evidence. Meta-analyses are considered the highest standard of evidence in medical research, although they are limited by the quality of the publications they analyze.

There is a high rate of false-positives in scientific research,² due primarily to misinterpreted statistics and publication bias (a tendency to both ignore contradictory data and preferentially publish positive results). This can sometimes be corrected by a meta-analysis, which may be able to detect confounding variables even when the primary research is not able to. It is related to Simpson’s paradox,³ wherein aggregate analysis demonstrates the *opposite effect* of many small studies.

In the context of cannabis, nearly all studies of cannabis and pregnancy are confounded by the use of tobacco or alcohol. Primary research, admittedly, often finds harmful effects in the cannabis

group. But aggregating many studies in a meta-analysis allows the true culprit (tobacco) to be properly controlled, and so the ostensible harms associated with cannabis disappear.

Evidence regarding adverse pregnancy outcomes

Three meta-analyses on cannabis and pregnancy outcomes have been published. They focus primarily on the effect of cannabis and tobacco on birth weight, as well as preterm birth and other indicators of babies' health. The most recent meta-analysis, published in 2016 by Connor *et al.*⁴ analyzed 31 separate studies. Comparing nearly 8,000 infants born from cannabis-using mothers to over 120,000 control babies, they conclude that “the association between maternal marijuana use and adverse pregnancy outcomes may be attributable to concomitant tobacco use and other confounding factors and **not marijuana alone**” [emphasis added].⁵ Unlike most of the primary sources they considered, their study was pre-registered, which is known to dramatically reduce the risk of false-positive results.⁶

Tobacco and cannabis are often used by the same groups of people. Since tobacco is a well-known teratogen, it is necessary to consider the possibility that higher rates of tobacco smoking among cannabis-using mothers could account for the risks often seen in primary research.

When Connor *et al.* first analyzed the data without accounting for tobacco use, they did, in fact, find an association between cannabis use and both low birth weight and preterm birth. There was a 40% increase in the risk of these two complications. But when they stratified their analysis based on tobacco use, the risk attributable to cannabis dropped to around 10% and lost its statistical significance. The authors also looked at a number of secondary measures of harm, such as spontaneous abortion (when the placenta detaches from the uterus). **Once again, no negative effects were attributable to cannabis when tobacco use was accounted for.**

The quality of a meta-analysis depends on the consistency of the primary research it considers. If the data are produced by widely different methods, a simple meta-analysis may not be appropriate. Heterogeneity is a statistical measure of whether the methods and results fail to be uniform; less heterogeneous data will be more consistent, and the ensuing conclusion of the meta-analysis will be more reliable. The publications used by Connor had significant heterogeneity, suggesting underlying differences in the studies' populations. But this heterogeneity was eliminated by simply accounting for tobacco use, implying that tobacco is a factor which fundamentally biases much of the primary research on cannabis in pregnancy.

Low birth weight & long-term effects

The first meta-analysis of cannabis's effect on developmental outcomes was published in 1997 by English *et al.*⁷ They analyzed ten studies, considering only publications that accounted for tobacco use among pregnant mothers. The results are quite similar to Connor *et al.*: they found cannabis was associated with a 9% increase in the risk of low birth weight, which was not statistically significant.⁸

English *et al.* highlight that there is a bias towards false-positive results. For example, one study did not report numbers for cannabis because there was no harmful effect; thus, this result showing safety could not be included in their analysis. It is notable that even though this publication bias promotes false-positive results, the meta-analysis was negative – it showed no statistical effect of cannabis. They concluded that “**there is inadequate evidence that maternal cannabis use, at the levels of consumption typically reported, causes low birth weight.**”

The final study on this topic, a 2016 meta-analysis published by Gunn *et al.*,⁹ is upfront about its limitations. “Determining a cannabis-only effect [on the fetus] was not possible ... it is unknown if the effects found in this manuscript are related to cannabis or are a by-product of alcohol and

tobacco use,” they caution.¹⁰ Their publication analyzes 24 studies and does attribute some harm to cannabis (a mean 109 gram decrease in birth weight, seventy-seven percent increased odds for low birth weight, higher risk of anemia, and other complications).

Unlike the studies by Connor and English, however, this report does not attempt to disentangle the known toxicity of tobacco from the postulated effect of cannabis. As a result, Gunn’s analysis does not clearly demonstrate reproductive toxicity attributable to cannabis use. The researchers explicitly acknowledge this: “By conclusion, the effects of cannabis on maternal and fetal outcomes remain generally unknown.”¹¹

The recent report by the National Academies of Sciences, Engineering, and Medicine stated that there is evidence for a statistical association between cannabis and low birth weight.¹² Their conclusion, however, was based exclusively on the study by Gunn *et al.* It is unclear why Connor’s meta-analysis was not considered.

In summary, accounting for tobacco use among pregnant women improves the quality of reviews and eliminates any ascertainable harms due to cannabis. The available research provides some evidence *against* the notion that cannabis causes pregnancy complications. All three meta-analyses conclude that harms *cannot* be attributed to cannabis, though they don’t definitively prove that no such harms exist. More research is warranted, but **current scientific results do not support the designation of cannabis, THC, cannabis extracts, or cannabis smoke as developmental toxins under Proposition 65.**

Project CBD could only find one other meta-analysis that assessed how prenatal exposure to cannabis affects development in humans.¹³ The study sought to predict the likelihood of future conduct problems. Only three studies on cannabis were included in the analysis. If cannabis caused an effect it was too small to be statistically detected. The researchers “report no clear effects of [in utero] cannabis” exposure on conduct problems.¹⁴ Hence, **there is not sufficient evidence to suggest that cannabis causes long-term adverse developmental outcomes.**

Commentary on preclinical research

If researchers are worried about harmful effects of cannabis in pregnancy, it is clearly unethical to intentionally expose pregnant women to cannabis. Preclinical research is an alternative to the cross-sectional and longitudinal studies on which the above meta-analyses are based. Despite many limitations, preclinical studies have shed light on an important direction for human research and harm reduction. **Although cannabinoids do not seem to cause adverse developmental outcomes, they might amplify the toxic effects of alcohol, nicotine, and other teratogens.**

Preclinical studies on mice and rats consistently indicate that activating the endocannabinoid system exacerbates fetal alcohol syndrome.^{15,16} Cannabinoids normally regulate cell death. In the combined presence of fetal growth factors and inflammatory molecules, cannabinoids may activate endogenous systems used to kill cancer cells.¹⁷ This leads to cell death and a magnification of teratogenic effects in preclinical models. In the absence of inflammatory chemicals like nicotine, however, cannabinoids do not appear to be intrinsically toxic.

This possible adverse synergy does not justify designating cannabis or cannabinoids as developmental toxins under Proposition 65, especially in light of the clinical data cited above. It does, however, suggest that **public health messages should be tailored towards pregnant women using multiple substances.**

Preclinical considerations also highlight the need to base conclusions on well-designed studies that properly account for tobacco and alcohol use. If not, the potential synergy between cannabis and true toxins may be misinterpreted as an effect of cannabis itself.

Harming mothers and newborns

Claims regarding the potential dangers of cannabis use in pregnancy are part of a prohibitionist backlash against the increasing societal acceptance of cannabis as a safe medical and recreational substance. **Unsubstantiated dangers are promulgated under the guise of caution, rather than in the interest of public health.** But research into harm reduction shows that the stigmatization and criminalization of pregnant drug users worsens the lives of both the children and their parents.

Misplaced fears are not inconsequential. **Designating cannabis and THC as reproductive toxins under Proposition 65 would misdirect public health and harm reduction efforts away from known teratogens, like alcohol and tobacco.** It would erect yet another barrier to scientists trying to research the medical value of cannabis and cannabinoids. And it would amplify the single greatest harm that cannabis can cause to mothers and infants: intervention from Child Protective Services.

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