

# **Cannabis and the Reproductive System, Pregnancy and Development of Children**

**An extract from 'Cannabis: A General Survey of its Harmful Effects'.  
Mary Brett updated March 2020**

In the mid-seventies animal experiments suggested that cannabis adversely affects the secretion of gonadal hormones in both males and females, and the foetal development of animals given THC during pregnancy (Bloch 1983, Nahas 1984, Nahas and Frick 1987, Wenger et al 1992).

Research was triggered by the reporting of gynecomastia (breast development) in 3 young men (23 to 26) all heavy cannabis users (Harmon 1972). These findings are now in doubt as a small case-controlled study failed to find a relationship in 11 cases and controls (Cates and Pope 1977), and Mendelson (1984) said there would surely be more cases as the number of young men using cannabis was high.

Kolodny and others investigated men who were chronic cannabis users in 1972. They had reduced plasma concentrations of testosterone, sperm count and motility, with an increased number of abnormal sperm. Bloch 1983, Wenger 1992, and The National Academy of Science 1982, gave support to all his findings with experiments on animals.

Wenger said they were either due to the action of THC on the testes and/or the brain hormones that stimulate sperm production.

Kolodny's results were contradicted by Mendelson and others in 1974 in a large well-controlled study of heavy users. Other studies have produced positive and negative findings of the effect of THC on testosterone.

Although the reductions in testosterone and sperm numbers observed in some studies may not be of great significance in healthy adults, Hollister (1986) argued that they could pose problems in pre-pubertal males. A boy of 16, smoking cannabis since the age of 11, suffered from retarded development of the secondary sexual characteristics and growth. Partial recovery was attained 3 months after stopping (Copeland et al 1980). Also men with already impaired fertility may be at risk.

Dr Lani Burkman of Buffalo University Medical School, New York, reported to the annual meeting of The American Society of Reproductive Medicine in San Antonio, Texas on October 13th 2003. She had looked at the sperm of 22 frequent cannabis users (14 times a week for at least 5 years) and compared it with that of 59 men, non-users who had children. She found that the sperm were moving too fast, too soon. They would "burn out" before they reached the egg and would be unable to fertilise it. She suggested this may be a cause of infertility. She also found the users produced fewer sperm.

Studies on female fertility have also produced conflicting results. Bloch found that on exposing non-pregnant animals to THC, there was interference with the hormones concerned in reproduction produced in the brain. Oestrus was delayed, as was ovulation by a reduction of luteinising hormone and an increase in prolactin secretion. Rozenkrantz (1985) said exposure of pregnant women to THC was too risky as it may damage the foetus. Conflicting results have also been obtained on the cycling of sex hormones and duration of menstrual cycles in women.

The blastocyst stage of the embryo has to be implanted in the uterus wall for its continued development. Anandamide, the neurotransmitter mimicked by THC is produced at a high level in the uterus before implantation and then down-regulated at the time of implantation. High levels of anandamide induce spontaneous pregnancy loss in women. The use of cannabis at this crucial time during pregnancy may have the same effect (Paria et al 2001, Wang et al 2003).

A paper in 2006 (Klonoff-Cohen et al) on the effects of marijuana use on the outcomes of IVF (In Vitro Fertilisation) and GIFT (Gamete Intra-Fallopian Transfer) fertility treatments found that the prospect of a good outcome is reduced if either of the partners uses marijuana. Females produced fewer eggs and the child had a significantly lower birth weight, the more recent the use, the worse the effects. Male marijuana use was also associated with lower birth weight. Both timing and amount of the drug used

negatively affected IVF and GIFT.

The risk of miscarriage or ectopic pregnancy of women smoking cannabis in the early stages of pregnancy was highlighted in recent research by Dey and others in 2006. Anandamide controls the development of the embryo so the level of the neurotransmitter is crucial. THC by mimicking anandamide disrupts the correct signaling process. The embryos of mice treated with THC had more cell abnormalities than the controls and the embryos failed to travel to the uterus.

THC passes through the placenta in animals and humans, so it could potentially damage the embryo (Bloch 1983, Blackard and Tennes 1984). It is also passed in breast milk (Astley and Little 1990).

Experiments on animals have shown a number of very serious effects on gestation of offspring born to females given THC during pregnancy. These results must lead to a consideration of the possibility of similar effects occurring in humans (Abel 1985). In another paper in 1985 Abel found that a combination of alcohol and marijuana caused 73% fetomortality (offspring deaths) in rats and 100% in mice.

There is now consistent evidence to show that habitual cannabis smoking during pregnancy is associated with a lower than average birth weight (Hatch and Bracken 1986, Zuckerman et al 1989, Sherwood et al 1999) and height (Zuckerman et al 1989 and Tennes 1985) the relationship persists after control for confounding variables. Gibson and his colleagues in 1983 looked at the cases of 36 women, using cannabis 2 or more times/week. Twenty five per cent of them had premature births. An increased risk of prematurity was also found by Sherwood et al 1999.

Earlier experiments before the mid-eighties, not surprisingly produced inconsistent results as they were often conducted with insufficient care.

In 1995 Shiono and others failed to find any significant association between marijuana smoking and birth weight, however when the mothers blood was tested a clear tendency towards lower birth weight was apparent.

An analysis of 10 different studies into the effects of cigarette smoking in 1997, 7 of which involved cannabis use, displayed only a weak association between cannabis use and birth weight. For any use of the drug the average reduction was 48g. Use 4 times a day averaged 131g loss of weight. They concluded that the difference was small compared to the effects on birth weight of tobacco smoking, and that there is inadequate evidence that cannabis at the amount typically consumed by pregnant women, causes low birth weight (English et al 1997).

There are enormous problems in conducting surveys of this type. Heavy use of cannabis during pregnancy is rare, many samples are too small (Greenland et al 1982a/b, Fried 1980). Because of its illegality, many women are unwilling to be honest about their drug taking so lots of them will be classed as non-drug users (Zuckerman et al 1989). They are also likely to use alcohol, tobacco and other illegal drugs and tend to belong to a different social class (Fried, 1980, 1982, Tennes 1985). But the greatest problem is small numbers.

In 2002 the Avon Longitudinal Study of Parents and Children team in Bristol (Fergusson et al) looked at 12000 mothers expecting single babies. On average the babies were 216g lighter for women smoking once a week, they were significantly shorter and had smaller heads. When other factors were taken into consideration the average reduction in weight dropped to 90g. They equated the effect of a weekly joint to that of 15 cigarettes.

In animals very high doses of marijuana were needed to increase the rate of malformations occurring in the offspring. And indeed some experiments found this association (Linn et al 1983). Bloch (1983) found that in sufficient dosage, re-absorption, growth retardation and other malformations occurred in rats, rabbits mice and hamsters. But most of the best-designed studies failed to confirm these findings. Zuckerman et al in 1989 discovered among 202 infants, pre-natally exposed to marijuana, a rate of malformations no higher than in a control group of non-using mothers. Gibson et al 1983, Hingson et al 1982 and Tennes et al 1985, uncovered no increase in the rate of major congenital abnormalities in children born to marijuana-using mothers.

Abel (1985) and Bloch (1983) suggested the malformations may be due to reduced nutrition due to the very high doses of the drug. Hollister (1986) added that “Virtually every drug that has ever been studied for dysmorphogenic effects has been found to produce these if the dose is high enough, enough species are tested or the treatment is prolonged”.

However many of the papers that exonerate cannabis use were conducted using marijuana and not THC at the start of the eighties when the THC content of the marijuana widely used was very low. And Hall and others warned in 1994 that, “It would be unwise to exclude cannabis as a cause of malformation until larger and better-controlled studies have been carried out”.

Malformations could of course be caused by chromosome damage. It has not been possible to show that THC can produce effects on specific genes which can cause abnormalities (Hall 1994, Hollister 1986). Cannabis smoke on the other hand is mutagenic (Bloch 1983). Hollister (1986) and The Institute of Medicine (1982) both discounted evidence that cannabinoids may cause mutations.

Three studies in the late eighties and early nineties linked cannabis use to an 11-fold increase in the cases of one form of leukaemia, ANNL (Acute Nonlymphoblastic Leukaemia) born to mothers using cannabis during pregnancy and increases in two other forms of childhood cancer, rhabdosarcoma and astrocytomas (Robison et al, 1989 Neglia et al 1991, Grufferman et al 1993). The children with ANNL were younger than children with the disease born to non-using mothers and had cell differences which the researchers said made it unlikely that the relationship was due to chance.

There is little literature on the subject of the development of children whose mothers had smoked cannabis while pregnant. One study, unique in its longevity, The Ottawa Prenatal Prospective Study has been carried out from 1978 to the present day by Dr Peter Fried and his team. The children were examined neurologically immediately after birth and again several times in their first year. Tests for cognitive and psychomotor functioning were then executed yearly. At first, signs of neurological development deficiencies were detected, a delay in the development of the visual system and an increased rate of tremors and startle, as were withdrawal symptoms. These disappeared and nothing was reported till the age of four when memory and verbal ability were found to be deficient. At 5 and 6 these seemed to have gone but the six year olds had impaired ability to sustain attention. From 6 to 9, several deficits in cognitive functions were noted and the parents reported behavioural problems. Between 9 and 12, there was a reduced ability as “regards memory in connection with visual stimuli, analytical ability and integrative ability”. Again attention maintenance was a problem. The same pattern emerged from 13 to 16 (Fried 2003).

Fried et al in 1992 found that marijuana use increases the symptoms of ADHD in first grade children. Six year old children are more likely to show signs of this condition if their mothers smoked 6 or more marijuana cigarettes /week.

Fried said that the damage inflicted by cannabis at the foetal stage would not be noticed until the child needed to use his or her “executive” functions (for problem-solving and planning) at the age of four. Leavitt et al (1994) and Lundqvist (1995) found similar deficits in adult cannabis users. Fried also warns that the marijuana in 1978 when his investigation began had a much lower average THC content, so the risks may now be higher. On 15th July 2006 Dr Fried is due to give a talk at The 13th World Conference on Tobacco OR Health in Washington DC. As part of his long running study, he will say that children of mothers who smoked marijuana while pregnant are more than twice as likely to take up the habit when they reach adolescence.

Dahl (1995) had found sleeping problems in 3 year olds and Day (1994) lower intelligence scores also at the age of 3. These findings support those of Fried.

Another long-term study has been published. Goldschmidt and others in 2002 gathered data from over 250 women who used cannabis while pregnant. Reports from parents and teachers were used and at age 6 the teachers reported problems with delinquent behaviour. At 10, questionnaires were distributed and interviews conducted. A clear relationship between exposure to cannabis and delinquency was established, manifested by attention deficits, impulsiveness and hyperactivity.

Tennes and others in 1985 studied over 200 women who had used cannabis during pregnancy. The children were monitored after birth and again at one year old. They failed to find any differences

between them and the controls.

An Italian research team under Vincenzo Cuomo (2003) injected pregnant rats with a low dose of artificial cannabinoid. The offspring were hyperactive. This disappeared at adulthood but was replaced by learning and memory retention problems. Because rats do not have confounding factors like tobacco smoking, standard of living or alcohol use, the results can be very useful. Fried said this showed great consistency with his study on humans.

The most recent study on the effects of pre-natal marijuana exposure (Day et al September 2006) has concluded that, "Prenatal exposure to marijuana, in addition to other factors, is a significant predictor of marijuana use at age 14". Other variables controlled for were: the child's current alcohol and tobacco abuse, pubertal stage, sexual activity, peer drug use, delinquency, family history of drug abuse and parental depression, current drug use, strictness and levels of supervision.

In 2002, Nahas and others reported that THC damages the formation of DNA in the dividing cells of testes and has been shown to impair the development of sperm cells in man. Marijuana or THC produces an early apoptosis of these fast-dividing cells and THC-induced apoptosis has also been found to occur in cells of the immune system (Zhu et al, 1998). Apoptosis is the "programmed cell death" of all our cells as they grow older, it is an irreversible biological process.

THC accumulates in fatty tissues and there are huge reserves of fat in the body for THC storage. With regular marijuana smoking the THC will build up quickly and take about 30 days to be completely eliminated. There will thus be a constant slow release of THC that will affect any processes going on in the body. Nahas concluded, "During chronic exposure to THC the pharmacokinetic molecular mechanisms which limit the storage of THC in the brain and testes are not sufficient to prevent a persistent deregulation of membrane signalling and the induction of functional and morphological changes which reflect a premature apoptosis of spermatogenic cells. Long-term longitudinal epidemiological studies have reported decreased spermatogenesis in healthy fertile adults".

Referring to 25-year old research findings on cannabis and the reproductive process detailed in his book *Marijuana and Medicine* 1999, Nahas said, "The latest studies in molecular biology have demonstrated that THC, the active ingredient in marijuana, damages the earliest stages of reproductive function. Thus marijuana is gametotoxic (toxic to embryos and sperm). It kills the reproductive cells of seven animal species, produces damage to the embryo, and retards foetal development. All of these destructive effects of marijuana on sperm cells, embryonic cells or lymphocytes have now been related to the early production of "apoptosis", the programmed death of the cell".

Frequent maternal marijuana use may be a weak risk factor for Sudden Infant Death Syndrome, SIDS (Scragg et al 2001).

In 2002 in The Princess Royal Maternity Hospital in Glasgow, drug tests (from the first stools) were carried out on 400 newly born babies. One in eight was found to have been exposed to cannabis in the womb. The study was carried out by forensic scientists from Glasgow University (Dr Ghada Abd-El-Azzim and Dr Robert Anderson), paediatric consultants (Lesley Jackson and Charles Skeoch) and senior registrar Scott Williamson. About 130 babies every year are treated at the hospital for drug dependency. Treatment can take days, weeks or months. According to the *Forensic Science International Journal*, more than 75% of babies exposed in this way will have medical problems later in childhood compared to 27% of the unexposed infants (Sunday Post 15/12/02).

A paper by Schuel et al in 2002 found evidence that anandamide signaling regulates human sperm functions required for fertilization. An analogue of AEA (anandamide) and also THC modulated capacitation and fertilizing potential of human sperm in vitro, sperm fertilizing capacity (in the Hemizona assay) was reduced by 50%. "These findings suggest that AEA-signaling may regulate sperm functions required for fertilization in human reproductive tracts, and imply that smoking of marijuana could impact these processes.

2002 Richardson and others looked at prenatal exposure to alcohol and marijuana and the effects on 10 year-old neuropsychological outcomes. At 10 over 500 children from a longitudinal study were tested for problem solving, learning, memory, mental flexibility, psychomotor speed, attention and impulsivity. Prenatal marijuana use had an effect on learning and memory as well as impulsivity.

2003 Williams et al looked at maternal lifestyle factors and risk for ventricular septal defects. Abstract: 'The Atlanta Birth Defects Case-Control Study was used to identify 122 isolated simple VSD cases and 3029 control infants born during the period 1968 through 1980 in the metropolitan Atlanta area. Exposure data on alcohol, cigarette, and illicit drug use were obtained through standardized interviews with mothers and fathers. Associations between lifestyle factors and VSD were calculated using maternal self-reports; associations were also calculated using paternal proxy-reports of the mother's exposures. RESULTS: Maternal self-report of heavy alcohol consumption and paternal proxy-report of the mothers' moderate alcohol consumption were associated with isolated simple VSD. A two-fold increase in risk of isolated simple VSD was identified for maternal self- and paternal proxy-reported cannabis use. Risk of isolated simple VSD increased with regular (three or more days per week) cannabis use for both maternal self- and paternal proxy-report, although the association was significant only for maternal self-report. CONCLUSIONS: This is the first study to identify an association between maternal marijuana use and VSD in offspring. Further studies are needed to elucidate this'.

2005 Gray et al looked at prenatal exposure and effects on depressive symptoms at age 10. 633 mother/child dyads were studied. Exposure to marijuana in the first and third trimesters predicted significantly increased levels of depressive symptoms (rather than a diagnosis of a major depressive disorder).

A review article was written in 2006 (Huizink and Mulder). They came to the conclusion; that pre-natal exposure to either maternal smoking, alcohol or cannabis use is related to some common neurobehavioural and cognitive outcomes, including symptoms of ADHD (inattention, impulsivity), increased externalising behaviour, decreased general cognitive functioning, and deficits in learning and memory tasks.

Bluhm et al in 2006 found that maternal recreational use of drugs and marijuana during pregnancy were associated with increased risk of neuroblastoma in offspring.

Barros and colleagues, writing in *The Journal of Paediatrics* in January 2007 found that marijuana-exposed infants born to adolescent mothers scored differently on measures of arousal, regulation and excitability compared to non-exposed infants, they showed subtle behavior changes in the first few days of life, they cried more, startled more easily and were more jittery. The authors said this may interfere with mother-child bonding.

Harkany et al in a paper in January 2007 found that endocannabinoid signaling modulates CNS (Central Nervous System) patterning so that "pharmacological interference with endocannabinoid signals during foetal development leads to long-lasting modifications of synaptic structure and functioning. Marijuana abuse during pregnancy can impair social behaviours, cognition and motor functions in the offspring with the impact lasting into adulthood.

Another paper in May 2007 had similar findings. Endocannabinoids in the human body play a vital role in the development of a baby's brain. They are responsible for controlling how the complex system of nerves develop in the embryonic brain. Dr Ann Rajnicek said "Smoking cannabis could interfere with the signals that are being used in the brain to wire it up correctly in the first place. As the brain develops further, there will be functional problems – potential brain damage" (Berghuis P et al 2007).

Forrester and Merz found selected birth defects with prenatal drug use in a study in Hawaii. December 2007. Cases were infants/fetuses with any one of 54 selected birth defects delivered during 1986-2002. Marijuana rates were significantly higher than expected for 21(39%) of the birth defects. These defects were associated with the CNS, cardiovascular system, oral clefts, limbs and the gastrointestinal system.

A paper in March 2008 by Goldschmidt et al found that intelligence test performance was adversely affected at the age of 6 in children born to cannabis-using mothers. 648 children were involved in the study. Women were questioned about their use of marijuana at 4 and 7 months of pregnancy and at delivery. The results were: 'There was a significant nonlinear relationship between marijuana exposure and childhood intelligence. Heavy marijuana use (one or more cigarettes per day) during the first trimester was associated with lower verbal reasoning scores on the Stanford-Binet Intelligence scale. Heavy use during the second trimester predicted deficits in the composite, short-term memory and quantitative scores. Third trimester heavy use was negatively associated with the quantitative score. Other significant predictors of intelligence include maternal IQ, home environment and social support'.

They concluded that, “These findings indicate that prenatal marijuana exposure has a significant effect on school-age intellectual development”.

2008 Aversa looked at erectile dysfunction in young habitual cannabis users. When cannabis is smoked, the arteries are constricted by a small amount. In long-term abusers, the arteries become so constricted that blood cannot properly flow to the penis. Men who chronically abuse marijuana show links to impotence since there is damage to the penile endothelium vasodilation and dilatation of brachial arteries. Dr. Aversa and his research team have concluded that, “early endothelial damage may be induced by chronic cannabis use (and endocannabinoid system activation).”

2008 April, Ian Russell, a specialist nurse practitioner in andrology and urology at Dumfries and Galloway Royal Infirmary in Scotland said, “ In my clinic I see youngsters from the age of 17 onwards with sexual dysfunction. The age of onset of smoking cannabis is young, 10 years old in some areas. Puberty’s kicking in and they’re smoking regularly – 5,6 joints a week. This can potentially suppress and traumatize the formation of leydig cells which secrete testosterone in the testes. This means these kids when they hit 14 or 15, will have sexual problems, for instance, not being able to get an erection, and possibly not having any sexual desire and a very very low testosterone level.

2008 Viagra is being prescribed for young men who use cannabis. The NHS in Scotland now spends £25m on Viagra, in some areas there is a 20% rise. There has been a rise in the number of teenage boys seeking help for erectile dysfunction. Two experts have now linked this increase with cannabis use. Ian Russell, an expert on sexual health at Dumfries and Galloway Royal Infirmary, revealed more Scottish teens than ever before are suffering impotence after smoking cannabis during puberty, and Derek Rutherford, a specialist in sexual medicine for NHS

2009 van Gelder et al looked at maternal preconceptional illicit drug use and the risk of congenital malformations. Abstract: We analyzed data from the National Birth Defects Prevention Study, a case-control study of major birth defects, and assessed all birth defects categories in which there were at least 250 interviewed case mothers. We included 10,241 infants with major congenital malformations (case infants) and 4,967 infants without major congenital malformations (control infants) born between 1997 and 2003 for whom there was a completed maternal interview with detailed information on prenatal illicit drug use and potential confounders. We used multivariable logistic regression to estimate the associations between cannabis, cocaine, and stimulant use in the month before pregnancy or during the first trimester (periconceptional period) and the occurrence of selected birth defects. In the periconceptional period, 5% of the 15,208 mothers reported any use of illicit drugs. We did not find associations between illicit drug use and most of the 20 eligible categories of congenital malformations. Periconceptional cannabis use seemed to be associated with an increased risk of anencephaly (adjusted odds ratio \_ 1.7; 95% confidence interval \_ 0.9 –3.4), whereas cocaine use in the periconceptional period was associated with the risk of cleft palate (2.5; 1.1–5.4). There were very few suggestions of positive associations between periconceptional illicit drug use and the 20 birth defects categories

I recently was in conversation with a midwife who had delivered babies of cannabis-using mothers. She said, “They are ravenous, chew their hands constantly, drink 3 times as much milk as non-affected babies, are promptly sick, then hungry again.

January 2010 El Marroun et al again found that maternal cannabis use even for a short period in pregnancy may be associated with lower birthweight and head circumference, and this this was more pronounced than the growth restriction seen in tobacco users. 7.5 thousand women were assessed.

2010 Gray et al: 86 pregnant women provided details of daily cannabis and tobacco use during pregnancy. Cannabis exposure was associated with decreased birth weight, reduced length and smaller head circumference, even after control for tobacco c-exposure.

2010 Campolongo et al looked at the developmental consequences of perinatal cannabis exposure - neuroendocrine and behavioural effects in adult rodents. Conclusions: ‘There is increasing evidence from animal studies showing that cannabinoid drugs are neuroteratogens which induce enduring neurobehavioral abnormalities in the exposed offspring. Several preclinical findings reviewed in this paper are in line with clinical studies reporting hyperactivity, cognitive impairments and altered emotionality in humans exposed in

utero to cannabis. Conversely, genetic, environmental and social factors could also influence the neurobiological effects of early cannabis exposure in humans'.

2010 Willford et al looked at prenatal tobacco, alcohol and marijuana, and their effects on processing speed, visual-motor coordination, and interhemispheric transfer. 320, 16-year olds, taking part in a longitudinal study into effects of prenatal substance exposure on development outcomes were investigated. No interactions were found between the 3 substances. Confounding factors were controlled for. There were significant and independent effects of the 3 on processing speed, and interhemispheric transfer of info. Tobacco and marijuana were implicated with deficits in visual-motor coordination.

2011 Shamloul reviewed the medical literature on cannabis use and sexual health. He revealed that cannabis use may negatively impact male sexual performance. While it was previously known that cannabis could affect certain receptors in the brain, it's now believed that these receptors also exist in the penis. Cannabis use may have an antagonizing effect on these receptors in the penis, making it more difficult for a man to achieve and maintain an erection.

2011 Day and others looked at the effects of prenatal marijuana exposure (PME) on delinquent behaviour. 580 mother/child dyads were used from the 4<sup>th</sup> prenatal month through 14 years. Offspring of heavier marijuana users were significantly more likely to report delinquent behaviour at age 14. The odds ratio for delinquency for those exposed to one or more joints per day during gestation was 1.76. PME significantly predicted child depressive symptoms and attention problems at 10, after controlling for other significant covariants. Child depressive symptoms and attention problems at 10 significantly predicted delinquency at 14 years. The association between PME and delinquent behaviour at 14 years was mediated by depressive symptoms and attention problems in the offspring at 10 years.

2011 Frank et al studied the impact of intrauterine exposure to substances on initiation of use by adolescents. 149 adolescents who had been exposed to cocaine in the uterus were followed from birth till the age of 16. Higher levels of IUCE (intrauterine cocaine exposure) were associated with a greater likelihood of initiation of any substance (licit or illicit) as well as marijuana and alcohol specifically. Those with lighter intrauterine marijuana exposure had a greater likelihood of initiation of any substance as well as of marijuana particularly. Time dependent higher levels of exposure to violence between ages 8 and 16 were also robustly associated with initiation of any illicit or licit use and of marijuana and alcohol particularly.

2011 April: Marroun and others found, using stats from over 4000 children that intrauterine exposure to cannabis is associated with behavioural problems in early childhood with an increased risk for aggressive behaviour and attention problems as early as 18 months in girls, but not boys. No association was found between cannabis use of the father and child behaviour problems.

2011 Keimpema and others looked at the pre-natal development of the neuronal system. Endo-cannabinoid signalling orchestrates neuronal differentiation programs through timed interaction with the cannabinoid receptors. Cannabis, through prolonged switching on of these receptors high-jacks the system and leads to the erroneous wiring of neural networks. Cannabis-induced cannabinoid receptor activity over-rides physiological neuro-developmental endo-cannabinoid signals affecting the timely formation of synapses.

2012 Jan, Goldschmidt and others found, in a longitudinal study from birth, that a significant negative relation was found between prenatal exposure to marijuana (PME) and 14 year old WIAT(Wechsler Individual Achievement Test) composite and reading scores. The deficit in school achievement was mediated by the effects of PME on intelligence test performance at 6, attention problems and depression symptoms at 10, and early initiation of marijuana use.

Psychoyos et al in 2012 August found that new high-potency marijuana can interfere with early brain development in developing foetuses. 'Some new high-potency strains, including some medicinal cannabis blends, contain up to 20 times more THC than did 'traditional marijuana from decades past' said Delphine.Psychoyos, the co-author. 'Easy access to drugs via the internet

or dispensaries makes the problem worse'. Harmful effects can begin as early as 2 weeks from conception. Exposure to today's marijuana in early pregnancy is associated with anencephaly, a devastating birth defect in which infants are born with large parts of the brain or skull missing. Early pre-natal use was also tied up with ADHD, learning disabilities, memory problems in toddlers and 10 year olds as well as depression, aggression and anxiety in the teens.

Lacson and others in September 2012 found that marijuana use may increase the risk of developing subtypes of testicular cancer that tend to carry a worse prognosis. This result should be considered not only in people using cannabis recreationally but also when marijuana and its derivatives are used for therapeutic reasons in young male patients. 163 young men diagnosed with testicular cancer were compared with 292 healthy men of the same age and race/ethnicity. The marijuana-using men were twice as likely to have subtypes called non-seminoma and mixed germ cell tumours. These cancers usually occur in younger men and carry a worse prognosis than the seminoma type. These results confirm those of 2 previous studies of marijuana and testicle cancer.

2013 Fiellin found that 'previous alcohol, cigarette and marijuana use were each associated with current abuse of prescription opioids in 18-25 year old men, but only marijuana use was associated with subsequent use of prescription opioids in young women'.

NHS Statistics Agency December 2013 showed that more than 20 babies/week are born addicted to drugs, including methadone in England. More than 10,000 newborns had to put into 'cold turkey' at birth. The number with 'neonatal withdrawal symptoms' has risen by 11% in the past 4 years to 1,129 last year.

2013 Varner et al found that smoking pot may double the risk for stillbirth. Cannabis, smoking, illicit drug use and second-hand smoke exposure are linked to an increased risk for stillbirth. 663 stillbirths were enrolled into the study and 1,900 live births. Cannabis increased the odds of stillbirth by more than twice as much - a 2.8-fold increase.

2013 Capogrosso et al investigated erectile dysfunction. They found that 1 in 4 men seeking help for newly developing erectile dysfunction (ED) was under 40, nearly half of them having a serious condition. ED is common among older men, the prevalence increases with age. Severe ED was found in 48.8% of younger patients and 40% of the older men. Compared with the older men, younger men had a lower average body mass index, a higher average level of testosterone in the blood and a lower rate of other medical conditions (9.6% cf 41.7%). They had also smoked cigarettes and used illicit drugs. Capogrosso P, Colicchia M, Ventimiglia E, Castagna G, Clementi MC, more frequently than older patients.

2014 Szutorisz et al Found that parental THC exposure leads to compulsive heroin seeking etc in the subsequent generation. ' Electrophysiologically, plasticity was altered at excitatory synapses of the striatal circuitry that is known to mediate compulsive and goal-directed behaviour. These findings demonstrate that parental history of germ-Szutorisz H, DiNieri THC exposure affects the molecular characteristics of the striatum, can impact offspring phenotype, and could possibly confer enhanced risk for psychiatric disorders in the subsequent generation'.

2014 Jan Jaques et al in a review of the literature, weeded out the myths of the pregnant woman and her child. Current evidence indicates that cannabis use both during pregnancy and lactation may adversely affect neurodevelopment, especially during periods of critical brain growth both in the developing foetal brain and during adolescent maturation, with impacts on neuropsychiatric, behavioural and executive functioning. Future adult productivity and lifetime outcomes may be influenced.

2014 June Pacey et al found that sperm shape and size in young men can be affected by cannabis use. Men who produced ejaculates with less than 4% normal sperm ( the current criterium for normal) were nearly twice as likely to have produced a sample in the summer months (June to August) or if they were below 30 or to have used cannabis in the 3 months prior to ejaculation. Alcohol and tobacco had little effect. (Men exposed to paint stripper and lead have similar problems).



2014 Day et al looked at PME (Prenatal Marijuana Exposure), age of marijuana initiation, and the development of psychotic symptoms in young adults. 763 pregnant women who completed the birth assessment in their fourth prenatal month, were selected for follow-up. Women and their offspring were followed till the offspring were 22 years of age (596 offspring were evaluated). PME and EAOM (Early Age Onset Marijuana) significantly predicted increased rates of PS (Psychotic Symptoms) at 22 years of age, controlling for other significant co-variants. They concluded that PME in addition to EAOM, may also play a role in the association between marijuana use and the development of PS.

2014 Warner et al investigated maternal-fetal health and the developing child. This is a summary of their findings: Evidence about the effects of marijuana use during pregnancy- and fetal-related complications and child development is inconclusive. Data from preclinical studies is suggestive of negative outcomes based on disruptive effects on the endocannabinoid system. The results from longitudinal, prospective studies that started in the late 1970s and early 1980s indicate subtle effects on attention, executive functions, and behavior, particularly as marijuana-exposed youth develop into adolescence and early adulthood. Given that today's marijuana is 6 to 7 times more potent and more likely to be consumed in greater average amounts by younger users, continued surveillance is warranted and may reveal more significant short-term and long-term harms. The practice of medicine for physicians who care for marijuana-using pregnant women is being shaped by shifting societal pressures. Increasingly, marijuana is being thought of as "medicine" by the general public as evidenced by "medical" marijuana laws. Pro-marijuana advocacy efforts may lead to perceptions about marijuana as being relatively "safe" and result in increased use by several groups, including pregnant women. At the same time, pregnant women who use illicit drugs and controlled substances such as prescription opioid analgesics are being criminalized and charged with child abuse and other felonies, despite efforts from scientists and medical professionals. Nationwide educational efforts are imperative to ensure women are not misled into believing that marijuana use in pregnancy is without possible danger to the developing fetus. Further research is critical to ascertain the specific risks to the developing fetus both in utero and beyond.

2015 Giacomo and others studied the CB2 receptors and spermatogenesis. They found that both hyper and hypostimulation of the CB2 receptors disrupted the temporal dynamics of the spermatogenic cycle. 'These findings highlight the importance of proper CB2 signalling for the maintenance of a correct temporal progression of spermatogenesis and suggest a possible adverse effect of cannabis in deregulating this process.'

2015 Warshak et al looked at the association between marijuana use and adverse obstetrical and neonatal outcomes. 6468 women, 6107 non-users and 361 marijuana users were included. They found that maternal marijuana use does not increase the risk of adverse obstetrical outcomes or fetal abnormalities, but does increase the risk for small for gestational age and neonatal intensive care unit admission.

2015 Roth et al looked at marijuana use by pregnant women. Approximately 4.4% of more than 67,000 pregnant women in the USA used illicit drugs while pregnant, marijuana being the most common. Marijuana can enter the bloodstream in seconds, the brain within minutes and cross the placenta to reach the fetus. Repeated marijuana use can alter receptors in the brain during fetal development as early as 2 weeks after conception, leading to problems with attention, memory and problem-solving. It can also affect an infant's birth weight, decrease length of gestation and increase risk for preterm labour.

2016 Carter et al looked at the effects of alcohol, methamphetamine and marijuana exposure on the placenta. All three were associated with distinct patterns of pathology. Marijuana was associated with larger placental weight.

2016 Gunn et al found that cannabis use in pregnancy was linked to low birth-weight and intensive care. Seven research data bases were researched up to 2014. 'Infants exposed to cannabis in the womb were 77% more likely to be underweight at birth and twice as likely to require intensive care'.

2016 Giacomo et al investigated fertility treatment for men. A cannabinoid receptor CB2 helps regulate the creation of sperm. Not only does this provide more evidence that marijuana can disrupt fertility in males, but it also suggests a therapeutic strategy for treating male infertility. Infertility is a worldwide problem that affect up to 15% of couples. Three groups of mice with different agents for 14 to 21 days. The first group was treated with a specific activator of the CB2 receptor. The second group was treated with a specific inhibitor of the CB2 receptor. The third group received only a saline solution and served as the control group. The group treated with the CB2 activator showed an acceleration of spermatogenesis, while the group treated with the inhibitor displayed a slower rate of the process. This suggests that a tight balance of CB2 activation is required for the proper progression of spermatogenesis. That the normal beneficial effects of endogenous cannabinoids on spermatogenesis

can be stimulated further by a chemical mimic, an agonist, is a potentially promising new idea for treating male infertility.

2016 Leemaqz et al studied maternal marijuana use and the risk for spontaneous pre-term birth. Women who continue to use marijuana at 20 weeks gestation are 5 times more likely to deliver pre-term than those who do not. Pregnancy outcomes for 5588 women in their first on-going pregnancy were studied, and interviewed at about 15 and 20 weeks of pregnancy. 236 women had spontaneous pre-term births, which is associated with the baby dying after birth or suffering long-term and costly health consequences. 4.5% of the participants used marijuana in the 3 months before pregnancy or during the first half of pregnancy.

2016 Chabarria et al explored marijuana and pregnancy. Out of 12,069 pregnant women, 106 reported using marijuana or marijuana plus tobacco. The combination of tobacco and marijuana had a significant effect on increased risk of multiple adverse perinatal outcomes, maternal asthma, pre-term birth, decreased head circumference, and decreased birth weight. Co-users also had elevated risks of pre-eclampsia.

2016 Goldschmidt et al looked at early marijuana initiation, the link between prenatal marijuana exposure, early childhood behaviour, and negative adult roles. PME (Prenatal Marijuana Exposure), child behaviour at 3, early onset of marijuana use ( EAOM <15) and adult roles at 22 were investigated. Early childhood behaviour was significantly related to EAOM . EAOM was significantly associated with negative adult roles, including being arrested, lower educational attainment, having a child outside marriage and unemployment at 22. Correlations between PME and negative adult roles and between early childhood behaviour and negative adult roles were also statistically significant.

2016 El Marroun et al looked at cannabis use in pregnancy and brain development in offspring. Children exposed to cannabis before birth had a thicker prefrontal cortex, a region involved in complex cognition, decision-making and working memory. The brains of 54 children, 6-8 years old, pre-natally exposed to cannabis were studied. Since they may also have been exposed to tobacco, 96 children exposed only to tobacco and 113 controls were used. Cannabis has different effects on the cortical thickness than tobacco.

2016 Health Canada warns of specific risks associated with the use of marijuana products for medicinal purposes. Under the age of 25 the product should not be used if allergic to cannabinoid or to smoke, have serious kidney, liver heart or lung disease, personal or family history of serious mental disorders – schizophrenia, psychosis, depression, bipolar disorder, are pregnant, planning to get pregnant or breast-feeding. ARE A MAN WISHING TO START A FAMILY, have a history of alcohol or drug abuse or substance dependence. Marijuana products can blood levels of testosterone, affecting sperm production, enough to render a person sterile. Even if a mother has never used cannabis, DNA damage from cannabis use can be passed on by father's sperm causing serious and fatal illnesses in offspring and may affect future generations. Marijuana may significantly increase a man's risk of developing an aggressive type of testicular cancer. Tends to strike between 20-25 and accounts for 40% of all testicular cancer cases.

2016 Friedrich et al looked at the effects of cannabis on embryological development. Use of marijuana in early pregnancy is associated with many of the same risks as tobacco. – miscarriage, birth defects, developmental delays, learning disabilities, but many more issues need addressing. THC alters molecular pathways that should not be disrupted during foetal development. The fact that THC seems to stop cancer growth by killing cancer cells suggests how damaging it could be to the foetus. The following findings were cited:

THC remains in the body for weeks, readily crosses the human placenta, THC levels have increased nearly 25-fold, THC interferes with the use of folic acid – deficiencies can lower birth weight, increase abortion rates, and cause neural tube defects e.g. spina bifida. Proper signaling for development and implantation of embryo is disrupted, and has been linked with autism and low IQ.

2016 Nielsen et al looked at abuse of alcohol and other illicit drugs and schizophrenia risk. Danish records of 3.1 million people's medical records were investigated. They found the increased risk of schizophrenia from cannabis (skunk) use was 5.2 times, alcohol 3.4, hallucinogenic drugs 1.9, sedatives 1.7, amphetamines 1.24. and other substances 2.8 times. **In a second study (Hjorthoj et al),** they found that pregnant cannabis-using women had children 6 times more likely to be schizophrenic.

For paternal cannabis use there was a 5.5 times increase risk of schizophrenia in the child before/after birth.

2016 Volkow et al looked at the risks of Marijuana Use During Pregnancy. Some cannabis extracts, THC and CBD have been passed for medical use. For example THC(dronabidol and nabilone) have been found to be effective in treating nausea. Increasing numbers of pregnant women are using medical marijuana to combat the nausea of pregnancy, particularly in the first trimester. Infants of women who used marijuana during pregnancy were more likely to be anemic, have lower birth weight and require neonatal intensive care than infants of non-users. Marijuana interferes with neurodevelopment, fetal brain growth and structural and functional neurodevelopment could be affected. The concentration of THC in marijuana has risen greatly in recent years. Physicians and other health care providers should warn about the risks of using marijuana during pregnancy.

2017 Mark et al looked at pregnant women and their cannabis use. Results: 'Of 306 surveys returned, 35% of women reported currently using cannabis at the time of diagnosis of pregnancy and 34% of those women continued to use. Seventy percent of respondents endorsed the belief that cannabis could be harmful to a pregnancy. Fifty-nine percent of respondents believed that cannabis should be legalized in some form and 10% reported that they would use cannabis more during pregnancy if it were legalized. Those who continued to use cannabis during pregnancy were less likely than those who quit to believe that cannabis use could be harmful during pregnancy (26% vs 75%). The most common motivation for quitting cannabis use in pregnancy was to avoid being a bad example (74%); in comparison, only 27% of respondents listed a doctor's recommendation as a motivation to quit'.

2017 Foeller et al looked at marijuana use in pregnancy. Abstract: Marijuana is the most commonly used illicit drug in pregnancy, and the prevalence of use during pregnancy is increasing in the United States. Although much of the existing research investigating marijuana use in pregnancy is limited by study design and confounding factors, a growing accumulation of data suggests adverse outcomes. Studies have identified associations with decreased birth weight, increased spontaneous preterm birth, and impaired neurodevelopment among children and adults with in utero exposure. Moderate concentrations of marijuana have also been identified in breast milk. Due to these findings, multiple professional societies have issued clear statements against marijuana use during pregnancy and lactation'.

2017 Callaghan et al investigated cannabis use and testicular cancer. 'The study included a population-based sample ( $n = 49,343$ ) of young men ages 18-21 years who underwent conscription assessment for Swedish military service in 1969-1970. The conscription process included a nonanonymous questionnaire eliciting information about drug use. Conscription information was linked to Swedish health and administrative registry data. Testicular cancers diagnosed between 1970 and 2011 were identified by International Classification of Diseases-7/8/9/10 testicular cancer codes in the Swedish National Patient Register, the Cancer Register, or the Cause of Death Register. No evidence was found of a significant relation between lifetime "ever" cannabis use and the subsequent development of testicular cancer [ $n = 45,250$ ; 119 testicular cancers]. "Heavy" cannabis use (defined as usage of more than 50 times in lifetime, as measured at conscription) was associated with the incidence of testicular cancer ( $n = 45,250$ ; 119 testicular cancer cases; The current study provides additional evidence to the limited prior literature suggesting cannabis use may contribute to the development of testicular cancer.

2017 Grant et al investigated the use of marijuana and other substances among pregnant and parenting women with substance use disorders and the changes in Washington State after marijuana legalization. 'In 2012, possession of marijuana for nonmedical use was legalized in Washington State. This study examined how legalization affected alcohol and drug use in a sample of pregnant and parenting women with substance use disorders. Study participants from nine counties in Washington State ( $N = 1,359$ ) were questioned about their substance use after completing a 3-year case management intervention program. The sample was divided into two cohorts based on whether participants had completed the program before or after legalization. Most study participants reported complete abstinence from alcohol and nonprescription drugs at program exit. Among those who were still using substances, women who completed the intervention after marijuana legalization were significantly more likely to report marijuana use at program exit compared with women who completed the intervention before marijuana legalization. Across both cohorts (pre- and post-legalization), we found a positive association of exit marijuana use with alcohol, illegal methadone, other opioids, amphetamines, and cocaine use; even when we controlled for historical period, the association with some of these substances with marijuana use remained evident. Independent of marijuana use, we saw increased use during the post-legalization period of alcohol, illicit methadone, and other opioids. Marijuana use at exit from the Parent-Child

Assistance Program (PCAP) increased significantly after marijuana legalization in the state. Women who were not abstinent from marijuana at program exit were likely to report use of other substances as well. Our study design demonstrates an association but does not allow us to conclude that marijuana use leads to other substance use among this sample of women with a history of polysubstance use.

2018 Crume et al looked at prenatal cannabis use and the association with low birth weights. Data from a survey of 3207 women who participated in the Colorado Pregnancy Risk Assessment Monitoring System in 2014-5. In Colorado the prevalence of marijuana use during pregnancy was 5.7% and 5% among those who were breast-feeding. They also discovered that prenatal marijuana use was associated with a 50% increased chance of low birth weight, regardless of tobacco use. Prenatal cannabis use was 3-4 times higher among those who were younger, less educated, in receipt of Medicaid or WIC, white, unmarried and poor. Between 2002 and 2014, cannabis use in pregnancy has increased 62% while potency has increased 6 or 7-fold since the 1970s. 88% of the women using cannabis were breast-feeding.

2018 Baker et al looked at the transfer of inhaled cannabis into human breast milk. OBJECTIVE: To evaluate the transfer of delta-9-tetrahydrocannabinol and its metabolites into human breast milk after maternal inhalation of 0.1 g cannabis containing 23.18% delta-9-tetrahydrocannabinol. A total of eight women were enrolled. Most were occasional cannabis smokers and one a chronic user. Delta-9-tetrahydrocannabinol was detected at low concentrations at all the time points beyond time zero. No metabolites were detected at any time point. Delta-9-tetrahydrocannabinol was transferred into mother's milk such that exclusively breastfeeding infants ingested an estimated mean of 2.5% of the maternal dose (the calculated relative infant dose=2.5%, range 0.4–8.7%). The estimated daily infant dose was 8 micrograms per kilogram per day. This study documents inhaled delta-9-tetrahydrocannabinol transfer into the mother's breast milk. Low concentrations of delta-9-tetrahydrocannabinol were detected. The long-term neurobehavioral effect of exposure to delta-9-tetrahydrocannabinol on the developing brain is unclear. Mothers should be cautious using cannabis during pregnancy and breastfeeding.

2018 Dickson et al Looked at recommendations from cannabis dispensaries about first-trimester cannabis use. Abstract: This was a statewide cross-sectional study in which advice about cannabis product use was requested using a mystery caller approach. The caller stated she was 8 weeks pregnant and experiencing morning sickness. Dispensaries were randomly selected from the Colorado Department of Revenue Enforcement Division website. The primary outcome was the proportion of marijuana dispensaries that recommended a cannabis product for use during pregnancy. We hypothesized that 50% of dispensaries would recommend use. A sample size of 400 was targeted to yield a two-sided 95% CI width of 10%. Secondary outcomes included the proportion endorsing cannabis use as safe during pregnancy, specific product recommendations, and encouraging discussion with a health care provider. Recommendations were compared by licensure type (medical, retail, or both) Of the 400 dispensaries contacted, 37% were licensed for medical sale (n=148), 28% for retail (n=111), and 35% for both (n=141). The majority, 69% (277/400), recommended treatment of morning sickness with cannabis products (95% CI 64–74%). Frequency of recommendations differed by license type (medical 83.1%, retail 60.4%, both 61.7%,  $P<.001$ ). Recommendations for use were similar for dispensary location (urban 71% vs nonurban 63%,  $P=.18$ ). The majority (65%) based their recommendation for use in pregnancy on personal opinion and 36% stated cannabis use is safe in pregnancy. Ultimately, 81.5% of dispensaries recommended discussion with a health care provider; however, only 31.8% made this recommendation without prompting. Nearly 70% of Colorado cannabis dispensaries contacted recommended cannabis products to treat nausea in the first trimester. Few dispensaries encouraged discussion with a health care provider without prompting.

2018 Schuetze et al looked at prenatal cannabis use and infant size and behaviour. 'Nearly 30 percent of women who smoke cigarettes during pregnancy also report using marijuana,' says Rina Das Eiden, PhD, RIA senior research scientist. "That number is likely to increase with many states moving toward marijuana legalization, so it's imperative we know what effects prenatal marijuana use may have on infants." Eiden studied nearly 250 infants and their mothers. Of these, 173 of the infants had been exposed to tobacco and/or marijuana during their mothers' pregnancies. None were exposed to significant amounts of alcohol. Eiden found that infants who had been exposed to both tobacco and marijuana, especially into the third trimester, were smaller in length, weight and head size, and were more likely to be born earlier, compared to babies who were not exposed to anything. They also were more likely to be smaller in length and weight compared to babies exposed only to tobacco in the third trimester. The results were stronger for boys compared to girls. "We also found that lower birth weight and size predicted a baby's behavior in later infancy," Eiden says. "Babies who were smaller were

reported by their mothers to be more irritable, more easily frustrated and had greater difficulty calming themselves when frustrated. Thus, there was an indirect association between co-exposure to tobacco and marijuana and infant behavior via poor growth at delivery. "Furthermore, women who showed symptoms of anger, hostility and aggression reported more stress in pregnancy and were more likely to continue using tobacco and marijuana throughout pregnancy. Therefore, due to the co-exposure, they were more likely to give birth to infants smaller in size and who were more irritable and easily frustrated. The infants' irritability and frustration is also linked to mothers who experienced higher levels of stress while pregnant. "Our results suggest that interventions with women who smoke cigarettes or use marijuana while pregnant should also focus on reducing stress and helping them cope with negative emotions," Eiden says. "This may help reduce prenatal substance exposure and subsequent behavior problems in infants."

2018 Bolhuis et al studied maternal and paternal cannabis use during pregnancy and the psychotic-like experiences in the offspring. Abstract: Cannabis use continues to increase among pregnant women. Gestational cannabis exposure has been associated with various adverse outcomes. However, it remains unclear whether cannabis use during pregnancy increases the risk for offspring psychotic-like experiences. In this prospective cohort, we examined the relationship between parental cannabis use during pregnancy and offspring psychotic-like experiences. Comparisons were made between maternal and paternal cannabis use during pregnancy to investigate causal influences of intra-uterine cannabis exposure during foetal neurodevelopmental. This study was embedded in the Generation R birth cohort and included N = 3692 participants. Maternal cannabis exposure was determined using self-reports and cannabis metabolite levels from urine. Paternal cannabis use during pregnancy was obtained by maternal report. Maternal cannabis use increased the risk of psychotic-like experiences in the offspring (ORadjusted = 1.38, 95% CI 1.03-1.85). Estimates were comparable for maternal cannabis use exclusively before pregnancy versus continued cannabis use during pregnancy. Paternal cannabis use was similarly associated with offspring psychotic-like experiences (ORadjusted = 1.44, 95% CI 1.14-1.82). We demonstrated that both maternal and paternal cannabis use were associated with more offspring psychotic-like experiences at age ten years. This may suggest that common aetiologies, rather than solely causal intra-uterine mechanisms, underlie the association between parental cannabis use and offspring psychotic-like experiences. These common backgrounds most likely reflect genetic vulnerabilities and shared familial mechanisms, shedding a potential new light on the debated causal path from cannabis use to psychotic-like phenomena. Our findings indicate that diagnostic screening and preventative measures need to be adapted for young people at risk for severe mental illness.

2018 Jansson et al looked at perinatal marijuana use and the developing child. Increasing public attention has recently been paid to the opioid epidemic and attendant effects on prenatally exposed infants and children.<sup>1</sup> Current literature has emerged proposing marijuana as a safe alternative to opioids in addressing pain<sup>2</sup> and cannabis legalization as a way to decrease opioid fatalities.<sup>3</sup> As a result, perceptions of cannabis safety have increased, and the prevalence of marijuana use among pregnant women has expanded; past-month cannabis use among pregnant US women increased from 2.4% to 3.9% between 2002 and 2014.<sup>4</sup> Further, cannabis potency has been substantially increasing over the past 4 decades in the United States, and will likely continue to do so as extraction procedures of active components improve.

2018 Bertrand et al investigated breast milk for cannabinoid concentrations. Abstract: Marijuana is the most commonly used recreational drug among breastfeeding women. With legalization of marijuana in several US states and a 1990 study in which authors documented psychomotor deficits in infants breastfed by mothers using marijuana, there is a need for information on potential exposure to the breastfed infant. Our objective with this study was to quantify cannabinoids in human milk after maternal marijuana use. Between 2014 and 2017, 50 breastfeeding women who reported marijuana use provided 54 breast milk samples to a research repository, Mommys Milk. Concentrations of  $\Delta$ -9-tetrahydrocannabinol ( $\Delta$ 9-THC), 11-hydroxy- $\Delta$ -9-tetrahydrocannabinol, cannabidiol, and cannabinol were measured by using liquid chromatography mass spectrometry electrospray ionization.  $\Delta$ 9-THC was detectable in 34 (63%) of the 54 samples up to ~6 days after last reported use; the median concentration of  $\Delta$ 9-THC was 9.47 ng/mL (range: 1.01-323.00). Five samples had detectable levels of 11-hydroxy- $\Delta$ -9-tetrahydrocannabinol (range: 1.33-12.80 ng/mL) or cannabidiol (range: 1.32-8.56 ng/mL). The sample with the highest concentration of cannabidiol (8.56 ng/mL) did not have measurable  $\Delta$ 9-THC. Cannabinol was not detected in any samples. The number of hours since last use was a significant predictor of log  $\Delta$ 9-THC concentrations (-0.03; 95% confidence interval [CI] -0.04 to -0.01;  $P = .005$ ). Adjusted for time since last use, the number of daily uses and time from sample collection to analysis were also significant predictors of log  $\Delta$ 9-THC concentrations (0.51; 95% CI

0.03 to 0.99;  $P = .039$ ; 0.08; 95% CI 0.00 to 0.15;  $P = .038$ , respectively).  $\Delta^9$ -THC was measurable in a majority of breast milk samples up to ~6 days after maternal marijuana use.

2018 Ryan et al conducted a review of marijuana use during pregnancy and breastfeeding and its implications for neonatal and childhood outcomes. Abstract: Marijuana is one of the most widely used substances during pregnancy in the United States. Emerging data on the ability of cannabinoids to cross the placenta and affect the development of the fetus raise concerns about both pregnancy outcomes and long-term consequences for the infant or child. Social media is used to tout the use of marijuana for severe nausea associated with pregnancy. Concerns have also been raised about marijuana use by breastfeeding mothers. With this clinical report, we provide data on the current rates of marijuana use among pregnant and lactating women, discuss what is known about the effects of marijuana on fetal development and later neuro-developmental and behavioral outcomes, and address implications for education and policy.

2018 Sokol et al looked at maternal cannabis use during a child's lifetime to see if it associated with earlier initiation. Abstract: Mother and child data were from the National Longitudinal Survey of Youth 1979 (1980-1998 waves) and Child and Young Adults (1988-2014 waves) cohorts, respectively. Cox proportional hazard models assessed the effect of maternal cannabis use prior to a child's adolescence on the child's risk of subsequent cannabis initiation. Models were stratified by race and child's age category (6-16, 17-24,  $\geq 25$  years). Adjusted analyses controlled for sociodemographic variables. Analyses were conducted in 2017. Median age of cannabis initiation for children of maternal ever users was age 16 years compared with age 18 years among children of maternal never users. Children of 1-year and multiple-year users were at increased risk of cannabis initiation between ages 6 and 16 years (hazard ratio=1.38,  $p < 0.001$ , and hazard ratio = 1.45,  $p < 0.001$ , respectively). Effects were slightly stronger among non-Hispanic non-black children. As cannabis legalization expands across the U.S., adult use may become increasingly normative. This study indicates that maternal cannabis use may be a risk factor for early initiation among their offspring. Preventive interventions should consider strategies to delay initiation among children of cannabis users.

2018 Murphy et al looked at Cannabinoid exposure and altered DNA methylation in rat and human sperm. Abstract: Little is known about the reproductive effects of paternal cannabis exposure. We evaluated associations between cannabis or tetrahydrocannabinol (THC) exposure and altered DNA methylation in sperm from humans and rats, respectively. DNA methylation, measured by reduced representation bisulfite sequencing, differed in the sperm of human users from non-users by at least 10% at 3,979 CpG sites. Pathway analyses indicated Hippo Signaling and Pathways in Cancer as enriched with altered genes (Bonferroni  $p < 0.02$ ). These same two pathways were also enriched with genes having altered methylation in sperm from THC-exposed versus vehicle-exposed rats ( $p < 0.01$ ). Data validity is supported by significant correlations between THC exposure levels in humans and methylation for 177 genes, and substantial overlap in THC target genes in rat sperm (this study) and genes previously reported as having altered methylation in the brain of rat offspring born to parents both exposed to THC during adolescence. In humans, cannabis use was also associated with significantly lower sperm concentration. Findings point to possible pre-conception paternal reproductive risks associated with cannabis use.

2019 Young-Wolff et al Looked at self-reported daily, weekly and monthly cannabis use among women before and during pregnancy Abstract: Cross-sectional study using data from 367 403 pregnancies among 276 991 women 11 years or older who completed a self-administered questionnaire on cannabis use during standard prenatal care in Kaiser Permanente Northern California from January 1, 2009, to December 31, 2017. The annual prevalence of self-reported daily, weekly, and monthly cannabis use among women before and during pregnancy was estimated using Poisson regression with a log link function, adjusting for sociodemographics. Data analyses were conducted from February to May 2019. EXPOSURES: Calendar year. MAIN OUTCOMES AND MEASURES: Self-reported frequency of cannabis use in the year before pregnancy and during pregnancy assessed as part of standard prenatal care (at approximately 8 weeks' gestation). RESULTS: Among the overall sample of 367 403 pregnancies among 276 991 women, 35.9% of the women self-reported white race/ethnicity; 28.0%, Hispanic; 16.6%, Asian; 6.0%, African American; and 13.5%, other. In the sample, 1.2% of the women were aged 11 to 17 years; 15.3%, 18 to 24 years; 61.4%, 25 to 34 years; and 22.0%, older than 34 years. Median (interquartile range) neighborhood household income was \$70 472 (\$51 583-\$92 643). From 2009 to 2017, the adjusted prevalence of cannabis use in the year before pregnancy increased from 6.80% (95% CI, 6.42%-7.18%) to 12.50% (95% CI, 12.01%-12.99%), and the adjusted prevalence of cannabis use during pregnancy increased from 1.95% (95% CI, 1.78%-2.13%) to 3.38%

(95% CI, 3.15%-3.60%). Annual relative rates of change in self-reported daily cannabis use (1.115; 95% CI, 1.103-1.128), weekly cannabis use (1.083; 95% CI, 1.071-1.095), and monthly or less cannabis use (1.050; 95% CI, 1.043-1.057) in the year before pregnancy increased significantly, with daily use increasing most rapidly (from 1.17% to 3.05%). Similarly, annual relative rates of change in self-reported daily cannabis use (1.110; 95% CI, 1.089-1.132), weekly cannabis use (1.075; 95% CI, 1.059-1.092) and monthly or less cannabis use (1.044; 95% CI, 1.032-1.057) during pregnancy increased significantly from 2009 to 2017, with daily use increasing most rapidly (from 0.28% to 0.69%). Results of this study demonstrate that frequency of cannabis use in the year before pregnancy and during pregnancy has increased in recent years among pregnant women in Northern California, potentially associated with increasing acceptance of cannabis use and decreasing perceptions of cannabis-associated harms.

2019 Petrangolo et al investigated cannabis abuse or dependence during pregnancy. Abstract: A retrospective population-based cohort of births in the United States between 1999 and 2013 was created using data from the National Inpatient Sample. Births to mothers who reported cannabis dependence or abuse were identified using ICD-9 codes, and the effect on various obstetrical and neonatal outcomes was assessed using logistic regression, adjusting for relevant confounders (Canadian Task Force Classification II-2). RESULTS: A total of 12 578 557 births were included in our analysis. The incidence of cannabis abuse or dependence rose from 3.22 in 1000 births in 1999 to 8.55 in 1000 births in 2013 ( $P < 0.0001$ ). Women reporting cannabis dependence or abuse were more likely to have a preterm premature rupture of membranes (odds ratio [OR] 1.46; 95% confidence interval [CI] 1.35-1.58), a hospital stay of  $>7$  days (OR 1.17; 95% CI 1.11-1.23), and an intrauterine fetal demise (OR 1.50; 95% CI 1.39-1.62). Neonates born to exposed mothers had a higher risk of prematurity (OR 1.40; 95% CI 1.36-1.43) and growth restriction (OR 1.35; 95% CI 1.30-1.41). CONCLUSION: Cannabis use during pregnancy steadily increased over the study period. Users of cannabis during gestation were more likely to have adverse outcomes during delivery and require longer periods of hospitalization. Neonates born to exposed mothers were more likely to be born preterm and underweight.

2019 Corsi et al looked at the association between self-reported prenatal cannabis use and maternal, perinatal and neonatal outcomes. Population-based retrospective cohort study covering live births and stillbirths among women aged 15 years and older in Ontario, Canada, between April 2012 and December 2017. EXPOSURES: Self-reported cannabis exposure in pregnancy was ascertained through routine perinatal care. MAIN OUTCOMES AND MEASURES: The primary outcome was preterm birth before 37 weeks' gestation. Indicators were defined for birth occurring at 34 to 36 6/7 weeks' gestation (late preterm), 32 to 33 6/7 weeks' gestation, 28 to 31 6/7 weeks' gestation, and less than 28 weeks' gestation (very preterm birth). Ten secondary outcomes were examined including small for gestational age, placental abruption, transfer to neonatal intensive care, and 5-minute Apgar score. Coarsened exact matching techniques and Poisson regression models were used to estimate the risk difference (RD) and relative risk (RR) of outcomes associated with cannabis exposure and control for confounding. RESULTS: In a cohort of 661 617 women, the mean gestational age was 39.3 weeks and 51% of infants were male. Mothers had a mean age of 30.4 years and 9427 (1.4%) reported cannabis use during pregnancy. Imbalance in measured maternal obstetrical and sociodemographic characteristics between reported cannabis users and nonusers was attenuated using matching, yielding a sample of 5639 reported users and 92 873 nonusers. The crude rate of preterm birth less than 37 weeks' gestation was 6.1% among women who did not report cannabis use and 12.0% among those reporting use in the unmatched cohort (RD, 5.88% [95% CI, 5.22%-6.54%]). In the matched cohort, reported cannabis exposure was significantly associated with an RD of 2.98% (95% CI, 2.63%-3.34%) and an RR of 1.41 (95% CI, 1.36-1.47) for preterm birth. Compared with no reported use, cannabis exposure was significantly associated with greater frequency of small for gestational age (third percentile, 6.1% vs 4.0%; RR, 1.53 [95% CI, 1.45-1.61]), placental abruption (1.6% vs 0.9%; RR, 1.72 [95% CI, 1.54-1.92]), transfer to neonatal intensive care (19.3% vs 13.8%; RR, 1.40 [95% CI, 1.36-1.44]), and 5-minute Apgar score less than 4 (1.1% vs 0.9%; RR, 1.28 [95% CI, 1.13-1.45]). CONCLUSIONS AND RELEVANCE: Among pregnant women in Ontario, Canada, reported cannabis use was significantly associated with an increased risk of preterm birth. Findings may be limited by residual confounding.

2019 Schrott et al found a gene linked to autism which undergoes changes in men's sperm after pot use. A specific gene associated with autism appears to undergo changes in the sperm of men who use marijuana, according to new research. The gene change occurs through a process called DNA methylation, and it could potentially be passed along to offspring.

2019 Fish et al investigated whether CBD, THC use during early pregnancy can disrupt fetal development. We tested whether cannabinoids (CBs) potentiate alcohol-induced birth defects in mice

and zebrafish, and explored the underlying pathogenic mechanisms on Sonic Hedgehog (Shh) signaling. The CBs,  $\Delta$ 9-THC, cannabidiol, HU-210, and CP 55,940 caused alcohol-like effects on craniofacial and brain development, phenocopying Shh mutations. Combined exposure to even low doses of alcohol with THC, HU-210, or CP 55,940 caused a greater incidence of birth defects, particularly of the eyes, than did either treatment alone. Consistent with the hypothesis that these defects are caused by deficient Shh, we found that CBs reduced Shh signaling by inhibiting Smoothed (Smo), while *Shh* mRNA or a CB1 receptor antagonist attenuated CB-induced birth defects. Proximity ligation experiments identified novel CB1-Smo heteromers, suggesting allosteric CB1-Smo interactions. In addition to raising concerns about the safety of cannabinoid and alcohol exposure during early embryonic development, this study establishes a novel link between two distinct signaling pathways and has widespread implications for development, as well as diseases such as addiction and cancer.

2020 Kharbanda et al looked at birth and early developmental screening outcomes associated with cannabis exposure during pregnancy. Abstract: To compare birth and early developmental screening outcomes for infants with and without in utero cannabis exposures. Observational cohort of women receiving prenatal care within a large health system, live birth between October 1, 2015 and December 1, 2017, and at least one infant visit. Cannabis exposure was through routine urine toxicology screen. Preterm birth, small for gestational age (SGA) birth, birth defects, and early developmental screening outcomes were assessed from birth and electronic health record data. Of 3435 women, 283 (8.2%) had a positive urine toxicology screen. In utero cannabis exposure was associated with SGA birth, adjusted rate ratio (aRR) 1.69 (95% confidence interval [CI]: 1.22-2.34). Abnormal 12-month developmental screens occurred in 9.1% of infants with in utero cannabis exposure vs. 3.6% of those with negative maternal screens, aRR 1.90 (95% CI: 0.92-3.91). Additional birth outcomes were not associated with in utero cannabis exposure. Exposure to cannabis during pregnancy may adversely impact fetal growth.

2020 Skelton et al investigated recreational cannabis legalization in the US and maternal use during the preconception, prenatal and postpartum periods. Abstract: In the United States (US), recreational cannabis use is on the rise. Since 2011, 11 states and the District of Columbia have legalized cannabis for adult recreational use. As additional states consider legalizing, there is an urgent need to assess associations between recreational cannabis legalization and maternal use in the preconception, prenatal, and postpartum periods—all critical windows for maternal and child health. Using cross-sectional data from the 2016 Pregnancy Risk Assessment Monitoring System, we assessed associations between state cannabis legalization and self-reported maternal cannabis use. Using logistic regression, we estimated the adjusted prevalence ratio (PR) of cannabis use during the preconception, prenatal, and postpartum period for women delivering a live-born infant in three states that had legalized recreational cannabis (Alaska, Colorado, and Washington) and three states that had not legalized (Maine, Michigan, and New Hampshire) by 2016. Our final sample size was 7258 women. We utilized 95% confidence intervals (CI) and a significance level of  $\alpha = 0.05$ . After adjustment for potential confounders, women who resided in states with legalized recreational cannabis were significantly more likely to use cannabis during the preconception (PR 1.52; 95%CI ranging from 1.28–1.80;  $p < 0.001$ ), prenatal (PR 2.21; 95% CI ranging from 1.67–2.94;  $p < 0.001$ ), and postpartum (PR 1.73; 95%CI ranging from 1.30–2.30;  $p < 0.001$ ) periods, compared to women who resided in states without legalized recreational cannabis. Although evidence about the effect of marijuana use during these periods is nascent, these findings show potential for increased incidence of child exposure to cannabis. Longitudinal research is needed to assess immediate and sustained impacts of maternal use before and after state legalization of recreational cannabis.

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