Diploma thesis

The use of cannabis during pregnancy and breastfeeding and its effects on the newborn – including effects on General Movements

submitted by

Finn Tijl Ziegler

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under the supervision of

PD Dr. med. Wolfgang Raith

Dr.in med.univ. Jasmin Pansy

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Affidavit

I hereby declare that the following diploma thesis has been written only by the undersigned and without any assistance from third parties. Furthermore, I confirm that no sources have been used in the preparation of this thesis other than those indicated in the thesis itself.

Graz, 15 November, 2018 Finn Ziegler eh

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Abbreviations

BCE – Before Common Era

CBD – Cannabidiol

CB_1 – Cannabinoid receptor type 1

CB_2 – Cannabinoid receptor type 2

ECS – Endocannabinoid system

e.g. – exempli gratia (for example)

FNASS – Finnegan Neonatal Abstinence Scoring System

GMs – General Movements

GMA – General Movement Assessment

i.e. – id est (that is)

IUGR – Intrauterine growth restriction

LBW* – Low birth weight

LKH – Landeskrankenhaus

NAS – Neonatal abstinence syndrome

NBAS – Neonatal Behavioural Assessment Score

NICU – Neonatal intensive care unit

P – p-value

pOR – pooled odds ratio

pMD – pooled mean difference

SPTB** – Spontaneous preterm birth

SAMHSA – Substance Abuse and Mental Health and Services Administration

SD – standard deviation

SGA*** – Small for gestational age

SIDS – Sudden infant death syndrome

THC – Tetrahydrocannabinol

<u>by definition:</u>

* if the birth weight is below 2500 g independent of gestational age

** a preterm delivery before 37 weeks of gestation

*** if the birth weight of a newborn is below the 10^{th} percentile relating to the gestational age (for each week of gestation there is another graph)

Abstract

Background: Cannabis is the most commonly used illicit drug worldwide. About 2% and 13% of women use cannabis during pregnancy (intrauterine cannabis-exposure) in the Western world. Researchers associate chronic cannabis-exposure as a risk factor for spontaneous-preterm-birth (SPTB) and small-for-gestational-age (SGA). Postnatal, there might be an increased risk of developing a neonatal abstinence syndrome (NAS) or a motor and cognitive retardation.

Objective: We evaluated the effect of intrauterine cannabis-exposure on newborns at the Division of Neonatology in Graz (Austria). Furthermore, the purpose is to conclude the state-of-the-art for intrauterine cannabis-exposure and its impact on newborns.

Methods: A literature search was conducted to form a narrative review, including 40 scientific articles and 14 other sources. We conducted a retrospective data analysis of newborns coded with NAS diagnosis (n=150;2000-2016) and identified newborns with exclusive intrauterine cannabis and possible concomitant tobacco-exposure. Along with weight and gestational age, the percentile rank was evaluated. We routinely assessed the Finnegan-Score, and since 2015 also the General Movements (GMs) in infants with NAS to assess the neurological function.

Results: According to the literature, the most significant effects of intrauterine cannabis-exposure are a threefold risk for an SGA and a risk of decreased birth weight (about 110g or rather 272g). Furthermore, there is a sevenfold increased risk for SPTB and a doubled risk for a NICU admission. Between 2000 and 2016 five newborns with cannabis-associated NAS were identified, thereof four in the last two years. Three had a mild NAS. Two infants with NAS got medication and were assessed by General Movement Assessment (GMA). The GMs were scored as abnormal (“poor-repertoire”) during the first weeks of life. After the third month of life they normalised. Finally, four of five infants were released to foster parents.

Conclusion: The state-of-the-art shows that intrauterine cannabis-exposure can cause an NAS. It remains uncertain if the Finnegan-Score is adequate to assess a cannabis-associated NAS. The GMs can be biased by the NAS symptoms during

the first weeks of life. At the Division of Neonatology in Graz a small increase, based on a small number of cases, was considered. The difficult social situation is notable.

Zusammenfassung

Hintergrund: Cannabis ist die am häufigsten konsumierte illegale Droge weltweit. In der westlichen Welt konsumieren zwischen 2% und 13% der Frauen Cannabis während der Schwangerschaft (intrauterine Cannabis-Exposition). Forscher assoziieren die intrauterine Cannabis-Exposition als einen Risikofaktor für Frühgeburtlichkeit (SPTB=Spontaneous preterm birth) und small-for-gestational-age (SGA). Postnatal besteht ein erhöhtes Risiko für ein Neonatales Abstinenzsyndrom (NAS) sowie für eine motorisch-kognitive Entwicklungsverzögerung.

Fragestellung: Wir untersuchten die Auswirkungen intrauteriner Cannabis-Exposition auf Neugeborene, anhand von Daten der Klinischen Abteilung für Neonatologie in Graz (Österreich). Diese Arbeit soll den neuesten Forschungsstand bezüglich intrauteriner Cannabis-Exposition und dessen Auswirkungen auf das Neugeborene zeigen.

Material und Methoden: Um eine narrative Übersichtsarbeit zu erstellen, wurde eine Literaturrecherche durchgeführt. Dabei wurden 40 wissenschaftliche Artikel und 14 weitere Quellen miteinbezogen. Es wurde eine retrospektive Datenanalyse, aller mit der Diagnose NAS aufgenommen Neugeborenen (n=150; 2000-2016) und eine Identifizierung von Neugeborenen mit ausschließlicher intrauteriner Cannabis- beziehungsweise mit möglicher gleichzeitiger Tabak-Exposition, durchgeführt. Neben Gewicht und Gestationsalter wurde die Perzentilenlage erhoben. Routinemäßig wurden alle Neugeborenen mit NAS mittels Finnegan-Score beurteilt. Zusätzlich wurde seit 2015 ein General Movements Assessment (GMA) zur Einschätzung der neurologischen Funktion durchgeführt.

Ergebnisse: Laut der Literaturrecherche, sind ein dreifach erhöhtes Risiko für ein SGA, ein um 110g beziehungsweise 272g verringertes Geburtsgewicht, ein siebenfach erhöhtes Risiko für ein SPTB und ein zweifach erhöhtes Risiko für einen Aufenthalt auf einer neonatologischen Intensivstation, die signifikantesten Auswirkungen während der Perinatalperiode.

Zwischen 2000 und 2016 konnten fünf Neugeborene mit cannabis-assoziiertem NAS identifiziert werden, wobei vier davon, in den letzten zwei Jahren identifiziert wurden. Drei davon machten ein mildes aber manifestes NAS durch. Zwei wurden medikamentös behandelt und mit dem GMA beurteilt, welches zunächst abnormal ("poor-repertoire") mit drei Monaten als normal befundet wurde. Schließlich wurden vier von fünf Kindern bei Pflegeeltern untergebracht.

Schlussfolgerung: Der aktuelle Forschungsstand zeigt, dass es bei intrauteriner Cannabis-Exposition zu einem milden NAS kommen kann. Des Weiteren ist unklar, ob der Finnegan-Score adäquat zur Beurteilung vom cannabis-assoziierten NAS ist. Die General Movements (GMs) können in den ersten Lebenswochen durch das NAS beeinträchtigt sein. Auf der Klinischen Abteilung für Neonatologie in Graz ist eine leichte Zunahme, bei insgesamt kleiner Fallzahl, zu verzeichnen. Auffallend ist die schwierige soziale Situation.

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1. Introduction

The present diploma thesis was written between October 2016 and October 2018 at the Medical University of Graz, Department of Paediatrics and Adolescent Medicine, Division of Neonatology.

It examines the epidemiological and clinical effects of cannabis (marijuana) use during pregnancy on newborns. Furthermore, the controversy over recreational and medical cannabis use concerning legalisation and societal acceptance will be discussed. An idea of future prospects for diagnosis and treatment is given. This investigation will be referred to various sources based on a literature search.

Moreover, case reports of five newborns which were born and treated at the Division of Neonatology of the University Hospital of Graz (Landeskrankenhaus, LKH Graz, Austria) will illustrate the difficulty for health care. General Movements according to Prechtl were analysed in two cases. The predictive value for the neurological impact after intrauterine cannabis exposure is studied. In addition, the suitability of the scoring system to evaluate withdrawal symptoms after maternal cannabis use is questioned. Furthermore, the confounding factor of polydrug use has to be discussed.

1.1 Neonatal abstinence syndrome and cannabis use

Since 2008, five women who have used cannabis during pregnancy occurred at the Department of Obstetrics and Gynecology at LKH Graz. One was hospitalised in 2008 and the others in 2015 and 2016. In three of these cases, the newborns have developed a neonatal abstinence syndrome (NAS). The intensity of the NAS was evaluated by the Finnegan Score, which influenced withdrawal treatment (section 2.3). Physical and neurological development was evaluated in the follow-up care. Two newborns were filmed and assessed by general movements according to Prechtl. All cases will be described in section 3.1 where the hospitalisation and the follow-up care are reported.

NAS is a drug withdrawal syndrome which is caused by a sudden discontinuation of chronic foetal exposure to cannabis or other addictive substances that were used regularly by the mother during pregnancy. According to Kocherlakota et al. by definition NAS means a “generalised multisystem disorder, which predominantly involves the central and autonomic nervous system, as well as the gastrointestinal tract” (1). NAS is a clinical diagnosis. Even though NAS is rarely life-threatening, significant illness and a prolonged hospital stay, associated with high health care costs can be the consequence (1).

In addition, data on impaired development of these children has increased in recent years, and so the diagnosis of NAS should not only be seen as a diagnosis of the neonatal period (2).

Since the 1970s Prechtl started to assess general movements. The General Movement Assessment (GMA) delineate the integrity of the young nervous system, focussing on endogenously generated – i.e. without sensory input – age-specific motor patterns (3).

It became the most sensitive and specific method to assess the integrity of the central nervous system, because the predictive power of the GMA is equivalent to MRI (white matter assessment) and superior to cranial ultrasound or neurological examination (4–7).

1.1.1. Clinical evaluation of the neonatal abstinence ayndrome

There exist several different scoring systems to assess the NAS after maternal opiate use. Today, the most commonly used system to quantify an NAS at term age newborns is the Finnegan Score. The Finnegan Score includes the most common 21 withdrawal symptoms originating from the neurological (e.g. tremor, seizures), vegetative (e.g. sweating, tachycardia), respiratory (e.g. tachypnoea, nasal flaring) or gastrointestinal system (e.g. diarrhoea, excessive sucking). These symptoms help to quantify the NAS. If the score is higher than 8 points (out of 52 points) after one examination or higher than 24 in sum (maximum score of the day) after two or three consecutive examinations after an interval of two or four hours, an NAS is diagnosed (figure 6 in part 5. Attachment).

1.2 General part

1.2.1 Relevance and Prevalence

In the European Union, 13,9% of young people (aged 15-35 years) have used cannabis at least once in the year 2016 (last year prevalence). 15 countries supported data, seven countries of them reported higher, six similar and two lower numbers in comparison to 2014 (8).

The use of cannabis in Austria has further increased in the last few years. The month prevalence (at least consumed once in the last month) for the age group between 15 and 59 years of age increased from 2% in 2003 to 6% in 2013. Data for the age group between 15 and 35 years from Austria are not available. 30% to 40% of the adolescents and young adults (aged 15-24 years) used cannabis at least once in their lifetime and 13% in the last year. Approximately 1% of the European population has a high-risk use (more than 20 days a month). A quarter of these are women and 70% were in the childbearing age (8,9).

For Austria, this number will be marginally lower than the European average. An important fact is that more than 80% of these women will interrupt their cannabis use before getting pregnant or during the first half of their pregnancy. This number was calculated on basis of the study of Leemaqz et al. The number of all cases of cannabis use during pregnancy divided through those who still use it after the 20th week of pregnancy (63/315=0.20) (10). It is to assume that the biggest cannabis-associated impact on the newborn, relating to NAS and spontaneous preterm birth (SPTB), takes place in the second half of the pregnancy (8).

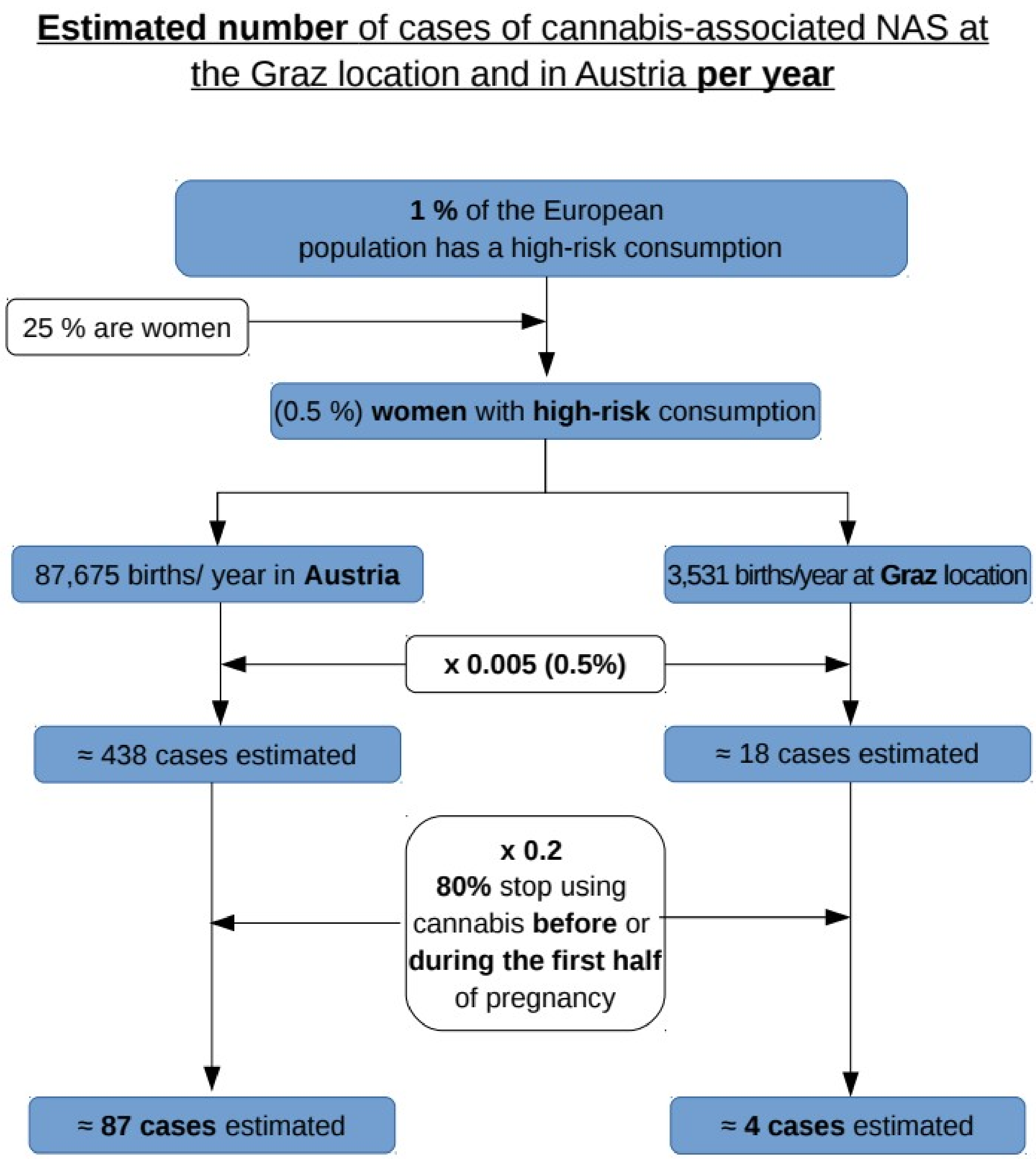


Figure 1: Flow chart: Estimated number of cases of cannabis-associated NAS at Graz location and in Austria per year

In Austria, it is to say that case numbers for cannabis-associated NAS are not existent. A simple estimation of expected cases with cannabis-associated NAS was made for the Graz location and for Austria. Starting with the average number of high-risk users for the EU, so 0,5 % of the women and 3500 births at the Graz location it is to calculate 18 exposed cases. In Austria there are 87,675 births and according to this 438 exposed cases (figure 1).Taking into account the 80% who interrupt their use, it is to calculate that approximately four women at the Graz location and 87 women in Austria are giving birth to a child who was notably cannabis-exposed and subsequently has a high risk to develop an NAS every year (11,12).

In the European health service, the number of first-time treatment of adolescents and adults for cannabis problems increased from 43,000 in 2006 to 76,000 in 2015. The reasons for this trend are an increased availability of high potency cannabis (subsection 1.2.6), a higher prevalence of cannabis use among the general population and bigger treatment provisions. As a consequence of the increase in cannabis use by women of childbearing age, a growing number of cases of NAS linked to cannabis use is expected (1,8).

The evidence for this trend has already been shown in a 20-year study in the U.S. by the national authority for Substance Abuse and Mental Health and Services Administration (SAMHSA) examining 420,665 pregnant women and their drug use from 1992 to 2012. Any kind of cannabis use increased from 29% (1992) to 43% (2012). The proportion of those indicating to consume regularly and mainly cannabis increased from 6% to 20% (13).

1.2.2 The history of cannabis as a psychoactive substance

The botanical name of “Cannabis” is the genus which belongs to the family Cannabaceae and to the class of flowering plants.

It has been used in China for the production of clothing, rope and Chinese medicine thousands of years BCE.

As far as is known cannabis was established in India as a narcotic drug and was spread across the Middle East to Europe. In Europe, the inebriating effect of cannabis became more popular in the 19^{th} century. The female cannabis plant contains Delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD). These are the two most important of 104 different active substances (cannabinoids) of the cannabis plant. They have psychoactive effects (14,15).

There are different species of cannabis: Cannabis sativa and Cannabis indica are the most widely spread. Today both are cultivated either as an inebriant or for industrial purposes. Cannabis sativa has a better fibre quality and Cannabis indica has a greater utility as an inebriant (14).

Cannabis or hashish are generally smoked pure or mixed with tobacco rolled as a cigarette (“joint”) or ingested via food and drinks. Cannabis is composed of dried flower buds, leaves and stems. Hashish is the extracted resin of the herbal components. The term “marijuana” is commonly used in the American and the term “cannabis” in the European linguistic usage. Thus, the term “cannabis” will be used in this thesis (14,16).

1.2.3 Difference between exclusive and concomitant cannabis use

When the term “exclusive cannabis use” is used in this thesis, it is about the mixed or pure use of cannabis by smoking or ingestion. Hence this means that cannabis can be mixed with tobacco but if tobacco cigarettes are additionally consumed, it is defined as “concomitant use”.

On the one hand in North and South America between 84% and 95.6% of the users smoke pure joints, thus only with cannabis. On the other hand, between 77.2% and 90.9% are mixing their joints with tobacco in Europe. Worldwide 65.6% of the cannabis users mix their joints with tobacco. That way of cannabis use is considered as exclusive (17).

Just one study was found, which investigated exclusive cannabis use. This is due to the fact that between 50% and 74% of the women who used cannabis, concomitantly smoked tobacco (10,18).

1.2.4 The cannabinoid system and the pharmacodynamics

This thesis focuses on THC and CBD which are the most important cannabinoids. THC is the most commonly known and relevant psychotropic constituent of the cannabis plant. CBD has less psychotropic effects and is more important for cannabis medicine due to fewer side effects. Normally, THC possesses the biggest part and CBD the second biggest part of cannabinoid-concentration in cannabis. Both cannabinoids can bind to the cannabinoid receptor type 1 (CB_1 receptor) and to the cannabinoid receptor type 2 (CB_2 receptor) of the endocannabinoid system (ECS). The effects on the human body are similar to endocannabinoids. “Cannabinoid receptors are found in various tissues throughout the human body, including brain and uterine decidua” (19).

In general, CB_1 receptors are located in the basal ganglia (or basal nuclei) and the hypothalamus. They induce euphorising, appetising and anti-convulsive effects and are essential for the control of voluntary motor movements, memory, regulation of body temperature and pain. CB_2 receptors are located at cells of the immune system and have anti-inflammatory effects (16,18).

The mode of action of THC and CBD have not yet been fully elucidated. It is to assume that there agonistic effects on the ECS for THC are more various, i.e. euphorising, analgesic, appetising or anti-convulsive and for CBD there are not euphorising, but anti-inflammatory and in contrast anti-psychotic (antagonism) (20).

For the gestation age at which the ECS is first detectable in the human embryo, two different dates were found. One source reported that the ECS begins to be active at 19th week of gestation (20) while two other sources could detect it starting from the 14th week of gestation (15,21).

Nevertheless, the ECS plays a crucial role for the human embryogenesis, thus before the 14th week of gestation. This could be shown in human placental studies where the CB_1 receptor was found in all the placental layers. Taking those facts

into consideration, it is to conclude that a “stimulation of these receptors will impair foetal growth by inhibiting cytotrophoblastic proliferation” (18).
THC is a lipophilic molecule with a small size that can easily pass many types of cell barriers, such as the blood-brain or placenta barrier. Animal studies have shown that THC concentrations in foetal blood and tissues are around 10% lower than the maternal plasma concentration (18).
The concentration in mother milk is even higher than in maternal plasma (subsection 3.2.7).

1.2.5 Potential effects on cannabis-exposed foetuses

The adverse effects of maternal cannabis use for newborns are:

a) short term: higher rates of SPTB, small for gestational age (SGA) or low birth weight (LBW), neonatal intensive care unit (NICU) admissions and smaller head circumferences
b) long-term: i.e. augmented numbers of psychomotor troubles concerning sleep, memory, attention, hyperactivity, learning skills, anxiety, depression and addiction.

1.2.6 Recent trends in THC and Cannabidiol concentrations

On one hand, an important trend for the last decades is the increasing concentration of THC in cannabis because of more variable and robust breedings which have been developed using hybrid technologies. For instance, in the U.S., the concentration for confiscated cannabis triplicated from 4% to 12% from 1995 to 2014. The psychotropic effects of THC can trigger psychotic diseases. On the other hand, the concentration of the antipsychotic substance Cannabidiol (CBD) decreases at the same time by the inverse proportion. In summary, the impact on cannabis-associated NAS remains unclear (22).

1.2.7 Legal situation

Today cannabis is the most commonly used illicit drug in the world. Until the end of 2015 any person found guilty of “acquiring, owning, producing, or introducing, carrying out delivering or providing cannabis to another person" in Austria was punished according to clause 27 of the Narcotics Law (23). According to this, exclusive use is not punished but in practice, this usually comes along with one of these prohibitions. From 2016 onwards the Narcotics Law tries to decriminalize the consumers by permitting to own and to acquire small quantities (<20 grams THC) for own use of cannabis. However, the condition for the abandonment of prosecution is the cooperation with a medical institution in the form of a therapy (24,25).

In May 2016, a drug dealing problem in Vienna's public areas got a big media response. Then, the law was tightened by a sentence for the dealers of up to two years of prison if they have dealt in public areas (26).

In other European countries, such as in Portugal (see below), The Netherlands and Spain the law is more liberal.

In 2001 Portugal passed a law which relieves owners of small quantities of psychoactive drugs (including heroin and cocaine) from prosecution. As a result, only serious drug crimes are avenged, the number of prisoners decreased by nearly 50% and there is more money left for preventive measures (27).

According to findings of H. Laqueur, the number of persons convicted and imprisoned for drug trafficking has fallen nearly 50% since the law permits "the acquisition, possession, and personal use of small quantities of all psychoactive drugs, including heroin and cocaine" (27).

The new program provides treatment, prevention and reintegration and at the post-reform period the self-reported cannabis use (except lifetime prevalence) did not rise (27).

In the U.S., the legalisation of cannabis has progressed further. After the ballots in November 2016, the medical use of cannabis is permitted in 28 states and the District of Columbia (D.C.). Further, eight U.S. states: i.e. California, Colorado, Alaska, Washington, Oregon, Massachusetts, Maine and Nevada, and D.C. have each legalised the recreational use of cannabis one by one since 2012 (22). About 60% of the U.S. population has access to medical cannabis and more than 20% to recreational cannabis (22,28).

Furthermore, there is a big industrial interest, above all in the U.S. does exist. According to Kurosch Yazdi the amount of taxes collected in the U.S. in 2016 by legal cannabis market was already more than 15%, with an upward trend, compared to the taxes of the tobacco market (14).

In summary, this trend is based on decrimalisation or rather legalisation of medical and in some cases recreational cannabis, increasing numbers of users in the past decade and as well increased treatment addmissions, considering cannabis-associated NAS and psychosis.

2. Methods

2.1 Literature search

Regardless the research strategy for literature was systematic in nature, it was not intended to assess the methodological quality or to pool data for meta-analysis. Articles were hand-screened and publications which matched inclusion criteria were synthesised into a narrative review.

From October 2016 to September 2017 the databases PubMed/Medline, The Cochrane Library and Google were searched for sources in English, German and French. The search was not restricted by publication date and conducted for articles, books and websites using the following keywords (separated or combinated) in each database: pregnancy, cannabis, marijuana, neonatal abstinence syndrome, General Movement Assessment or General Movements, prenatal effects, breastfeeding, Finnegan Score, prenatal drug exposure and THC (see part 6. Attachment). The results of the articles were restricted to primary research as randomised controlled, case-control, prospective and retrospective cohort studies. Furthermore, secondary research as systematic reviews and meta-analyses were also included. Most of the sources were from the field of paediatrics, obstetrics, drug prevention or social sciences.

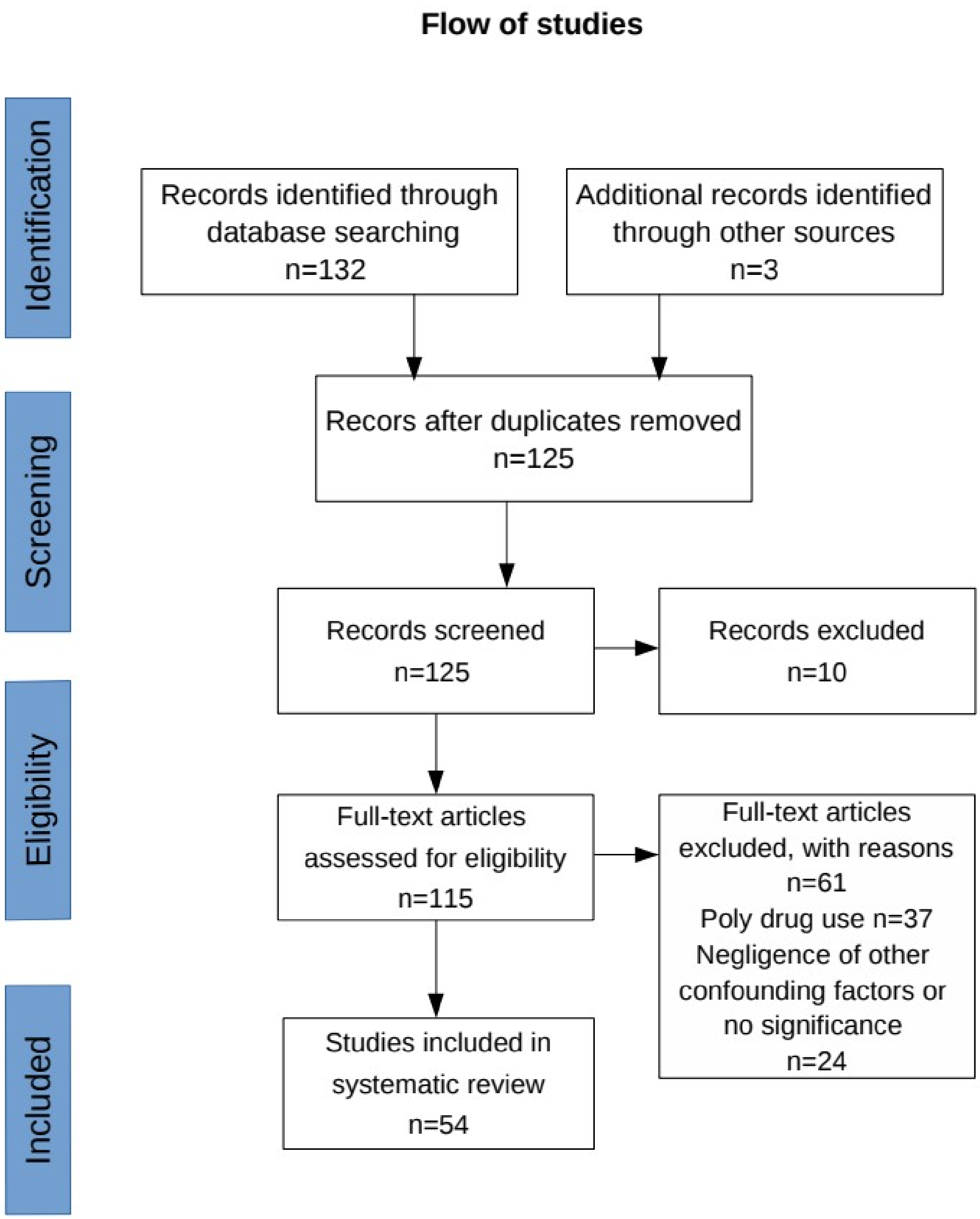
The literature search covered human and animal research but restricted cannabis, tobacco and alcohol use (in several cases). It was not possible to exclude tobacco use because only one study was found which compared an exclusive and concomitant use cohort and two which adjusted their results for exclusive cannabis use (10,29,30).

For the subsection 3.2.3 it was necessary to use one article with opiate-associated NAS (31). This is due to the fact that it was the only study which investigated prenatal drug exposure and a systematic GMA.

At large 90 articles were gained after removing duplicates. Of which ten were excluded at the first superficial screening. After a detailed assessment for eligibility, 40 were included and 40 were excluded due to an absent significance or no match on the topic of the review.

For primary research 17 retrospective and five prospective cohort studies, one randomised-controlled study, five state-of-the-art studies and three surveys were included. For secondary research eight systematic reviews and one meta-analysis were included.

Five books, seven reports and one conference proceedings were also included. Further, 24 websites were screened, while one was finally included.



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PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit www.prisma-statement.org.

Figure 2: Flow chart: Flow of studies

2.2 General Movement Assessment

2.2.1 Definition

General Movements (GMs) are spontaneous movements of the foetus, newborn and infant which occur without external stimulation and are generated endogenously by the nervous system.

GMs last up to a few minutes, involve the entire body and have a variable sequence. Above all the variable sequence of movements of the extremities, the neck and the trunk creates a complex movement pattern.

GMs come and go gradually, varying in intensity and speed. Rotations and frequent slight variations of the direction of motion make them look complex and smooth (31).

2.2.2 Historical review

Already at the end of the 19th century, spontaneous movements of newborns were observed. The first attempt to classify these movements was made by Irwin in 1930 (20). He was the first to describe the “newborn mass activity” as uncoordinated rapid mass movements of the newborn. Furthermore, Irwin showed that “the movements capture the entire body at such a speed that the observer cannot make a more precise distinction” (32).

Before 1980 only a few studies existed on spontaneous motor activity of healthy preterm and term newborns, based on bedside observation (33).

Thereafter, by the use of available video cameras, well-founded studies on spontaneous movements of the preterm and term newborns became possible. In the process, it turned out that these recordings were more eligible for the assessment of spontaneous motor activity than the direct observations (34).

Over the past 25 years, many articles on the spontaneous motor activity of foetuses, prematures and newborns have been published.

Reference values have been established and the assessment of the quality of the GMs as a sensitive and valuable method, has proven to be successful in appraising the integrity of the foetal and neonatal brain (34).

It should be mentioned that the same movement patterns can be observed for foetuses, preterm and term infants and therefore the same criteria can be used for the assessment (35).

2.2.3 Recordings of GMA

The newborn should lie in supine position and only wear a diaper. It has to be awake, without crying or fussing (active wakefulness) or the use of a pacifier. The recording should last up to ten minutes and the camera has to be positioned approximately one metre above the newborn at an angle of 45 degrees. The entire body with hands and feet must be visible in the screen, even if the newborn moves and stretches.

Einspieler et al. advise “not to record the GMs during the first three days after birth” (36). The newborn needs this time for adaptation, otherwise there will be a risk of a biased assessment.

Ploegstra et al. conducted an observational cohort study with healthy term age infants and came to the conclusion that the “GM quality normalised during subsequent days and was normal on day five to seven” (21).

2.2.4 Aspects of spontaneous movements

It is possible to observe foetal movements starting from the age of seven or eight weeks of gestation. From the age of nine to ten weeks of gestation, complex and generalised movements, so-called GMs or Startles occur.

Both movement patterns involve the entire body. GMs are slow and show complex movement sequences which concern all body parts. Startles are fast twitching and phasic movements of the hips, trunk and neck (36).

Between ten and twelve weeks of gestation, the repertoire of movements becomes richer. Patterns such as hiccup, breathing movements, yawning, head movements and stretching occur (37).

2.2.5 Classification of General Movements

2.2.5.1 “Normal” GMs

There are three types of GMs depending on the age of the infant (figure 3) (36):

preterm GMs	during the preterm age
writhing GMs	from term age until the end of the 2nd month after term
fidgety GMs	during the postterm age of 3 to 5 months (31)

Preterm GMs

Preterm GMs cannot be distinguished from foetal movements. But compared to movements around the birth date, they have a larger amplitude and a faster speed from time to time (38).

Writhing GMs

Term newborns and preterm infants approaching the birth date, show so-called Writhing Movements. They start from term age and go until the 2nd month after term. These are movements with moderate amplitude and velocity, which spread over the entire body. Fast and large stretching movements occasionally break through, especially of the arms. Writhing GMs are typified by a gestalt that is fragmentary or incomplete (39).

Fidgety GMs

In the third month after birth, major changes occur in the nervous system. The GMs change during this time. They loose their “writhing” quality and take on a “fidgety” character (39).

Fidgety GMs are small movements with a moderate velocity and variable acceleration of the neck, trunk and limbs in all directions (31).

They only occur in consciousness and when the infant is not crying. Normally they occur from the sixth to ninth week and remain until the 15th to 20th week of gestation (4).

Figure 3: Developmental course of general movements

The fidgety GMs disappear when a wilful motor activity becomes dominant. The movements of the healthy infant in all three types are variable, complex and fluent (36).

2.2.5.2 “Abnormal” GMs

If the young nervous system is damaged, the GMs lose complexity and variability. Abnormal writhing movements are classified as, “poor repertoire”, “cramped-synchronised” or “chaotic” GMs. This applies to both preterm and term infants for the first two months after birth.

Abnormal fidgety GMs can be either classified as abnormal or completely absent (40).

“Poor repertoire” GMs

The sequence of the successive movement components is monotonous and the movements of the different body parts do not occur in the normal rich and complex sequence.

“Cramped synchronised” GMs

The movements appear rigid and stiff. They lack the normal smooth and fluent character. All limb and trunk muscles contract and relax almost simultaneously.

“Chaotic” GMs

The movements of all limbs are of large amplitude and occur in a chaotic order without any fluency or smoothness. They consistently appear to be abrupt (5).

Abnormal fidgety GMs

Abnormal fidgety GMs appear to look like normal fidgety GMs, but with moderate to serious increased amplitude and velocity. Thereby they take on a jerky character (4).

The absence of fidgety GMs

Between six and 20 weeks after the date of birth, the training (formation) of fidgety GMs is absent. However, other movements can be observed (4).

2.3 Finnegan Score

First of all, assessment and diagnosis of NAS starts with clinical suspicion based on maternal history. In order to provide an objective way to identify and categorise infants with NAS, several scoring systems were proposed.

Currently, the Finnegan Neonatal Abstinence Scoring System (FNASS) is the most commonly used scoring scale. The FNASS provides cutoff points (3 continuous scores ≥ 8 or 2 continuous scores ≥ 12) for the identification of the infants that may require pharmacological treatment. In total 52 points can be reached (subsection 1.1.1 and figure 6 at chapter 6). For the case described in section The FNASS is a comprehensive and lengthy tool so there have been several attempts to modify it (41).

The Finnegan Score is necessary to modify the pharmacologic therapy during the withdrawal.

Although the Finnegan Score was originally developed for newborns with opiate-associated NAS, it is also used for cannabis-associated NAS at the Division of Neonatology of LKH Graz. However, there is no scoring system which is specifically designed for cannabis-associated NAS. Therefore, the question arises if the Finnegan Score is suitable to assess a cannabis-associated NAS or is it necessary to generate a new scoring system especially designed for this syndrome.

3. Results

3.1 Case reports

Since 2008, five cases (n=5) of newborns exposed intrauterine to maternal cannabis use were referred to the Division of Neonatology of LKH Graz. All cases were considered as NAS and three of them were treated correspondingly (figure 4). Case number two will be described explicitly and the other four cases in a shorter version. All cases are anonymised by initialisation and no birth dates are published.

In advance, it should be mentioned that all the newborns were fed via bottle with formula milk and were monitored during the whole hospital stay (Division of Neonatology). The GMs of two newborns were assessed. For three newborns withdrawal symptoms were evaluated by using the Finnegan Score. Today, all newborns except one are living in foster families. For further details, view the flowchart below (figure 5).

3.1.1 Case 1

VL (initials for anonymisation) was born at term (39+6 weeks) from a 17 years old mother. The birth weight was 3,692 g (75th percentile), length 54 cm (90th percentile) and head circumference (HC) 36 cm (75th percentile). The mother declared to have consumed cannabis and tobacco during pregnancy. This intrauterine exposure was confirmed by a drug screening of the newborns' faeces for THC. Withdrawal symptoms were only observed during a single night at the fifth day of life. The nurses noticed a period of restlessness and described the newborn as hypertonic, tremulous and sweaty. Probably it seems that it could not urinate, because no urine could be detected in the diaper. Nevertheless, this restlessness lasted briefly and the newborn was discharged a few days later. No special treatment was necessary.

3.1.2 Case 2

JS was born spontaneously at term (37+4 weeks) with a birth weight of 2,700 g (30th percentile), a length of 47 cm (40th percentile) and a head circumference of 32 cm (25th percentile) after the pregnancy went normal. The Apgar score was 9, 10 and 10 after one, five and ten minutes (9/10/10) and the umbilical cord arterial pH was 7.25, thus both values were in normal range. The oxygen saturation and heart rate were normal. The newborn's breathing was regular and sufficient. It had an explicit congestion of the face caused by the umbilical cord around the neck.

The mother (22 years) was smoking one pack of cigarettes per day and two to six joints per week during pregnancy. Although no drug screening was performed, the mother was compliant and we have to assume a high-dosed intrauterine cannabis exposure.

Therefore, the newborn was admitted to the Division of Neonatology. Four hours after birth the infant had developed mild withdrawal symptoms. The maximum Finnegan Score of the day was 7 points. A mild NAS was diagnosed and treated by oral application of 30 mg of Phenobarbital on the first day (figure 4) and after the third day of life physiotherapy was initiated.

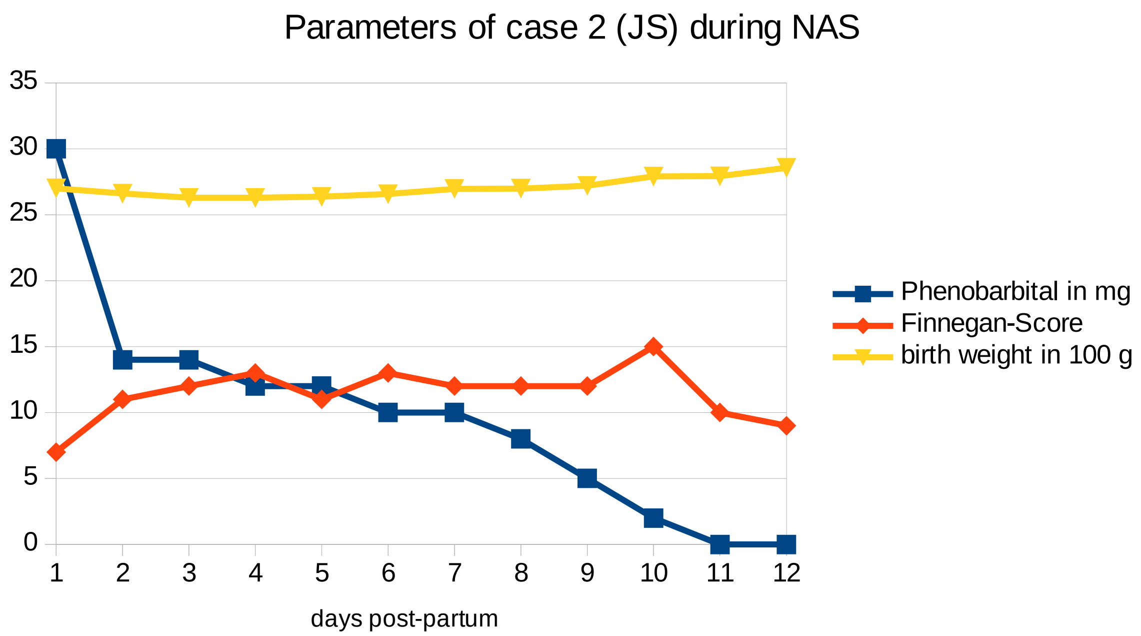

Figure 4: Parameters of case 2 (JS) during NAS

JS was frequently checked and the withdrawal was evaluated using the Finnegan Score. The main NAS symptoms were assessed with this score. The nurses noticed the following: “excessive sucking, hypertonic, irritated, is twitching in silence, loose stools, regurgitation, continuous high-pitched crying, sneezing, uncoordinated sucking and swallowing, mottling, higher temperature and sweating”. Strong sucking need and hypertonia were observed during the entire period. The hospital stay lasted 23 days.

The newborn was filmed three times during the writhing period at day five, ten and 15 of life for GMA. GMs were scored as “poor repertoire” at the global GMA. At the Detailed Scoring, it was assessed with a score of 22, 25 and 23.5 (day five, ten and 15; mean 23.5; standard deviation (SD) = 1.5) out of 42 points at General Movements Optimality Score (GMOS) which is according to the range for “poor repertoire” (median 25 [22–29]) according to Einspieler et al (6). Most of the presented deficits affected the movements of the upper extremities. GMs were poor in speed and amplitude range and had almost no proximal or distal rotatory components.Echo

In the followup, the newborn was filmed during the fidgety movement period. The fidgety movements were scored as “normal” with a maximum of Motor Optimality Score (28 out of 28 points).

JS was born with a lipomeningocele and after seven weeks of life, a systolic heart murmur was found during the examination at the follow-up care. Echocardiography ruled out a congenital heart defect.

Furthermore, in this examination, JS showed no sign of neurological dysfunction except a right-sided position asymmetry of the body. The weight was 4,410 g (50^{th} percentile), the length 54 cm (50^{th} percentile) and the head circumference 36 cm (25^{th} percentile).

To this first follow-up visit, JS came to the hospital, accompaigned by the biological mother. From the sixth 7 points month of life, the newborn was raised by a foster mother because the biological mother was not able to take care of it anymore. The foster mother attended JS in the second follow-up care examination. The foster mother reported that JS was in a good health condition and was eating and sleeping well at that time.

3.1.3 Case 3

LT was a term (39+0 weeks) newborn (birth weight 2,775 g (10^{th} percentile), length 48 cm (10^{th} percentile) and head circumference 33 cm (10^{th} percentile)) and the mother admitted, having continuously exposed it to cannabis and nicotine in utero. THC was detected in the mother’s urine, however, the newborn’s drug screening turned out to be negative for urine and stool. The liver function tests of LT were suspicious for alcohol abuse, but the performed Majewski Score to detect a foetal alcohol spectrum disorder turned out to be negative. After conspicuous myocloni, reflux and spitting a Finnegan Score was achieved for three days but the newborn did not score higher than 5 points for the single score. There was no pharmacologic therapy initiated. LT got physiotherapy during the whole hospital stay.

3.1.4 Case 4

RF was a full-term (39+1 weeks) newborn with 2,844 g (10th percentile) birth weight, 48 cm (10th percentile) length and 34,3 cm (30th percentile) head circumference. The mother delivered by Caesarean section. Due to a psychotic episode the mother was transfer to the psychiatry (closed ward). The medical history revealed a use of three to four joints a week since adolescence. In the past, the mother also used a benzodiazepine (oxazepam) to gain control over her full body pain. The mother reportedly claimed that “joints would help her more”. A drug screening of RF’s urine was negative. No withdrawal symptoms were observed. In the first 3 days of life, self-limiting oxygen desaturations were recorded with a minimum S_pO_2 of 61%.

3.1.5 Case 5

PW was born at term (38+4 weeks). Due to a birth weight of 2,320 g (< 3rd percentile), a length of 45 cm (< 3rd percentile) and a head circumference of 31.5 cm (< 3rd percentile), it was diagnosed to be SGA. Both, the mother and the newborn were tested positive for THC in the urine. The mother reported that she has or had smoked cannabis (one to two joints a week) and tobacco irregularly during pregnancy. A Finnegan Score was calculated and the maximum score of the day was 18 points a single score was 9 points. For three days the newborn was treated with Chloralhydrat and physiotherapy. It was filmed in terms of the GMA. Finally, it was released to the mother after evaluating the social situation by the social welfare.

PW was filmed once at day five of life to assess the GMs during the writhing period. The GMs were abnormal and classified as “poor repertoire” according to the global GMA. For the detailed GMOS the newborn scored 26 of 42 point which correlates with the range for “poor repertoire” (median 25 [22–29]) (6). It scored very poor at the upper extremities compared to the neck, trunk and lower extremities (7 out of 18 points). Its arms moved with a monotonous amplitude and speed and with a limited spatial range. PW had neither proximal nor distal rotatory components.

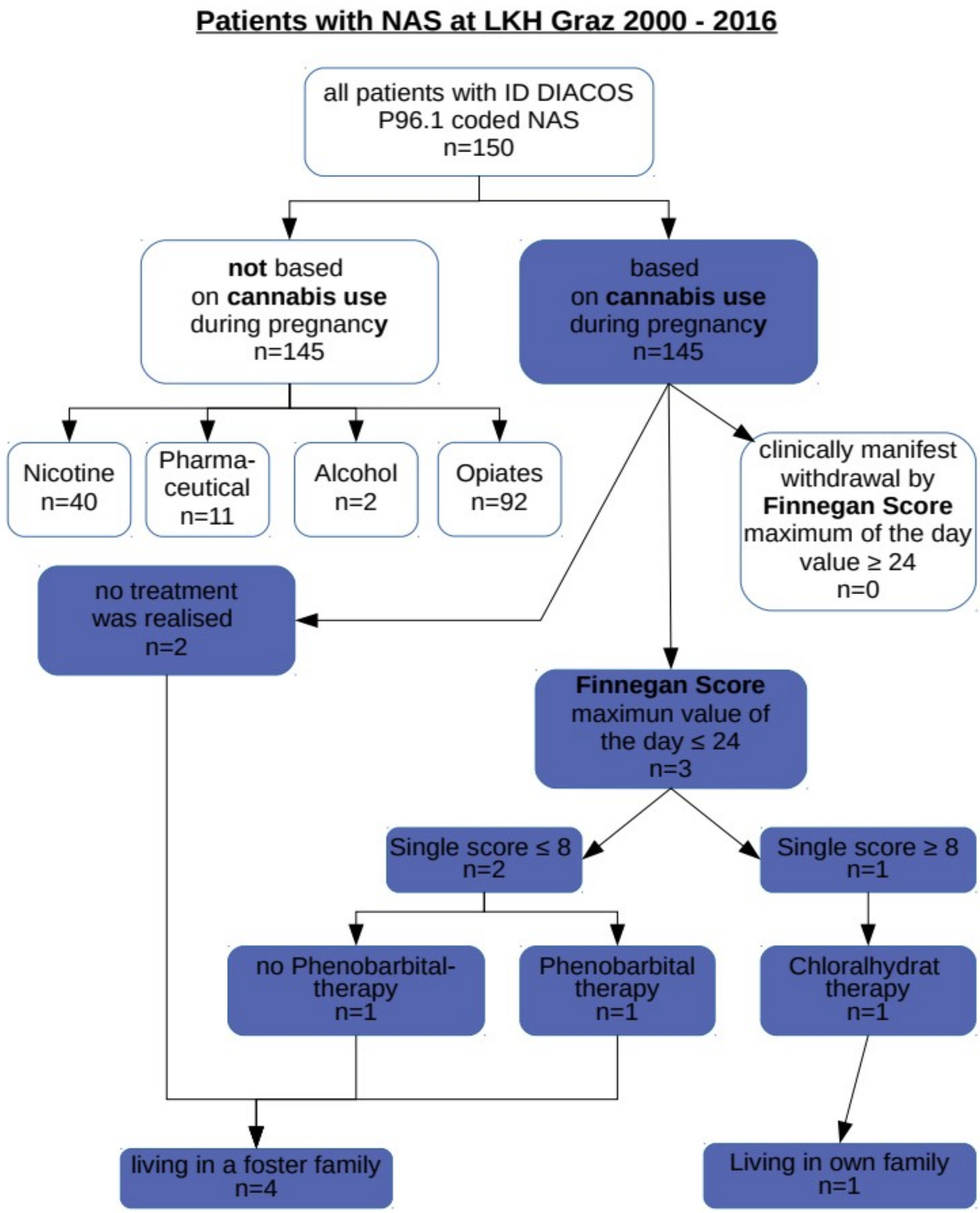

Figure 5: Flow chart: Patients with NAS at LKH Graz 2000 - 2016

3.1.6 Summary: mean values and scores

All newborns were born at term with a mean gestational age of 38+6 (SD=4 days) and had a mean birth weight of 2865 g (> 10th percentile; SD = 330 g). The mean length was 48.8 cm (> 10th percentile, SD = 2.2 cm) and the head circumference was 33.3 cm (> 10th percentile, SD = 1.5 cm) on average. Two newborns were female and three were male. In case 5 an LBW was diagnosed due to an IUGR or rather an SGA. No one had a microcephaly.

The Finnegan Score was evaluated for three newborns and had a mean scoring of 12.2, 14 and 16 respectively (sum of three scores in 24 hours). For two newborns no Finnegan Score was assessed because the NAS symptoms were developed neither long nor strong enough.

On an average, the newborns had an average length of hospital stay of nine days with a maximum stay of 23 days. The two pharmacologically treated newborns had a mean stay of 15 days (seven and 23 days). Three newborns were treated via physiotherapy.

Four infants were living in foster families at the moment of the last followup visit.

3.2 Literature

First of all, it should be mentioned almost 45% of the searched studies worked with women who reported their own cannabis use (seven of 16 studies). The others additionally used drug screening.

Nevertheless, screening by testing blood or urine is more sensitive than by self-report as demonstrated by Metz et al. They analysed a cohort of 1,610 women 2.7% of which had cannabis use during pregnancy. Amongst those 1.6% were detected by self-report and 1.9% using drug screening. Thus, in this study drug-screening was nearly 20% more sensitive than self-report. With the combination of both methods 2.7% could be detected (42).

Only one research project investigated exclusive cannabis use and compared it to concomitant cannabis use (subsection 3.2.4).

The review of Gunn et al. summarizes 24 articles which include 19 different studies of women who used cannabis during pregnancy. “In order to rule out effects of other illicit drugs (e.g. cocaine and opiates), only studies that reported outcomes of prenatal use of cannabis while excluding other illicit substances were included in this study” (43). However, due to the low number of studies which reported about exclusive cannabis use, studies reporting the effects of in utero exposure to cannabis in conjunction with alcohol and tobacco use were also included. The included infant outcomes were measured from the prenatal period to six weeks postpartum (43).

3.2.1 Effects around the perinatal period

The prospective cohort study of Leemaqz et al. analysed data from 5588 nulliparous women who were asked about their cannabis, tobacco and alcohol using habits during pregnancy. They reported their own substance use and were assessed for SGA, SPTB, preeclampsia, gestational hypertension and diabetes. The data was registered by the international SCOPE study (SCreening fOr Pregnancy Endpoints; New Zealand, Ireland, Australia and the UK). The participants were split in two groups: cases with pathologies called cases (n=1514) and those without called non-cases (n=4074) (10).

The self-reported substance use was recorded at 15 and 20 weeks of gestation. Hence, five categories were made: women who had no substance use (category 1), those who quitted before pregnancy (category 2), before 15 weeks (category 3), before 20 weeks (category 4) and those who did not quit at 20 weeks of gestation (category 5) (10).

In the cohort of cases, all with an SGA were considered in terms cannabis use: each category was compared to women who did not used cannabis. For category 5 the odds for the number of SGA cases were almost three times higher (1.9% : 0.7%) compared to women who had not used cannabis during pregnancy. The p-value (P) was 0.005, thus significant (10).

Considering the same constellation for an SPTB, the odds were almost seven times higher (4.7% : 0.7%) and the P < 0.001. At the cases of SPTB a reduction of the mean gestational age can be observed for these categories: 34.1, 33.8, 33.8, 33.4 and 29.6 weeks (10).

By taking a closer look at the gestational age of the cases with an SPTB, it is possible to observe that the newborns from category 5 were born after no more than 32 weeks of gestation (early SPTB). The total number of those cases was small (n=11). When comparing categories 1 and 5 the odds for early SPTB are approximately four times higher (15.8% : 63.6%). For the cases for very early SPTB (< 28 weeks of gestation), the odds are eight times higher (4.7% : 36.4%). “We have demonstrated that continued maternal use of marijuana at 20 weeks’ gestation is a major contributing risk factor for an SPTB” (OR 5.44) (10).

Demografic data

The pooled mean difference (pMD) of absolute birth weight after prenatal cannabis use was about minus 109.42 g. This was calculated on the basis of four studies, which showed a decrease in birth weight, whereas six studies showed a null association (four studies showed a decrease and 6 no association). For an LBW the researchers could detect a pooled odds ratio (pOR) of 1.77 times higher (seven studies showed an increase, two studies a decrease and five studies no association) (43).

The reported influence on an infant’s head circumference was a pooled mean difference (pMD) of minus 0.31 cm (four studies a decrease, six studies no association). The association for effects on neonatal length (two studies showed a decrease, six studies no association and one study an increase) and SGA (one study showed an increase and one study no association) were small. For intrauterine growth restriction (IUGR) no association was found (43).

Admissions to NICU

The necessity for a NICU admission was numbered by a pOR of 2.02 times higher (three studies showed an increase and one study no association). The pOR of spontaneous preterm birth (SPTB, <37 weeks of gestation) was 1.29 (times higher) (three studies showed an increase and six studies no association) (43).

From a population-based, prospective and randomised-controlled study (n=53 of the Generation R study) Marroun et al. recruited 6-year old newborns whose mothers used cannabis during pregnancy. The researchers made volumetric brain measures by MRI scans (44).

The MRI scan showed no association with altered global brain volumes (neither total brain, grey matter nor white matter volume). The only noticeable difference was in the thickness of the prefrontal cortex. For the cannabis-exposed newborns this cortex was thicker and for the tobacco-exposed newborns thinner. The importance of this fact is not evident. The researchers supposed that it has to cohere with reported problems in attention, motor control and working memory, which are located at this brain region. Thereby they also analysed the cohort's mean birth weight and found a significant (P=0.01) difference of minus 272 g on average compared to the control group without cannabis exposure in utero (3,203 ± 604 vs. 3,475 ± 520 g, P=0.003) (44).

3.2.2 Congenital anomalies

Minnes et al. report on physical variation concerning the eyes of infants. This study mentions "two abnormalities associated with the visual system: true ocular hypertelorism (widely spaced eyes) and severe epicanthus (skin folds at the corners of the upper eyelids) among infants whose mothers smoked more than five joints per week while pregnant" (45).

Van Gelder et al. adjusted under-reporting of maternal cannabis use with Bayesian models and showed a strong association with anencephaly (aOR = 2.2). Moreover an indication could be given for oesophageal atresia (aOR = 1.4), diaphragmatic hernia (aOR = 1.4) and gastroschisis (aOR = 1.2) (46).

There were three studies reviewed which did not explore an association with specific anomalies (18,22,29).

3.2.3 Association with GMs

A few associations of infants' spontaneous movements and prenatal cannabis exposure were found in three studies altogether:

In 1987, a study on 243 infants, Fried et al. reported that infants which were intrauterine exposed to cannabis had "decreased visual habituation along with an increased tremor, irritability and startle response", when analysed by Prechtl neurological examination. The researchers also reported on an association between in utero exposure to cannabis and increased hand-to-mouth activity, startles and tremor (47).

A research group led by Hayes et al. made a five-year follow-up of infants from Jamaica. Initially, they found no association between exposure to cannabis in utero and infants' scores on the Neonatal Behavioural Assessment Score (NBAS) in the first days after birth. However, at 30 days after birth those exposed to cannabis had lower automatic stability scores and higher scores on reflexes (subsection 3.2.8) (48).

As already mentioned in section 2.1 the study of Palchik et al. assessed GMs of 77 newborns with intrauterine opiate exposure for their GMs. An important confounding factor was that the newborns were exposed to HIV due to the mother's positive HIV status. For ten newborns of the cohort a active HIV-infection was detected. It is to assume that the intrauterine HIV has additional adverse effects on offspring (31).

The GMA in the writhing period of those newborns (77% of the cohort) revealed normal GMs in 30% of the cases, "poor repertoire" in 56% and "cramped-synchronised" in 8.5% (31).

Two months later in the fidgety period all newborns could be assessed and 67.5% showed "normal", 30% "abnormal" and 2.5% no fidgety GMs (31).

3.2.4 Comparison of the effects after exclusive or concomitant cannabis use

Most of the studies investigated concomitant cannabis use, i.e. cannabis use with additional and separate use of pure tobacco cigarettes. In the prospective cohort study of Leemaqz et al. it was reported that 74% of the women who used cannabis, also smoked tobacco as (10).

In the majority of the cases cannabis was used together with drugs (concomitant drug use), i.e. tobacco, alcohol and other illicit drugs like opiates and stimulants (e.g. cocaine, amphetamines). Jaques et al. report that almost half (48.9%) of cannabis-using women while pregnant, use tobacco (> 10 cigarettes per day), 12% opiates, 10% stimulants and 4 % have an alcohol-related diagnosis (18).

3.2.4.1 Concomitant cannabis use

Leemaqz et al. reported that there is no association with different perinatal outcomes of cannabis use due to concomitant tobacco use concerning an SPTB. “Breslow-Day test showed no evidence of heterogeneity in the association of marijuana use and pregnancy outcomes between smokers and non-smokers (P=0.238), which indicates that the association between marijuana and an SPTB was consistent regardless of cigarette smoking status” (10).

3.2.4.2 Exclusive cannabis use

It was possible to find one study, which investigated woman who had a gestational cannabis use whereby the cohort was split in a group of concomitant and exclusive use.

The study of Chabarria et al. assessed 12,069 patients whereof 0.88% were reporting cannabis use during pregnancy. 45% of the cannabis consuming group additionally used tobacco an were compared to the 55% of exclusive cannabis use. Surprisingly, the concomitant group showed a decreased head circumference (here <25th percentile) and birth weight (<25th percentile) compared to the exclusive group (29).

On the one hand, exclusive cannabis use was not associated with a significant decrease neither for head circumference (adjusted odds ratio (aOR) = 1.44; P=0.20) nor for birth weight (aOR = 1.09; P=0.76) (29).

On the other hand, concomitant cannabis use was oppositionally associated with higher odds ratios for a decreased head circumference (aOR = 2.34; P=0.006) and additionally with a significant p-value for decreased birth weight (aOR= 2.79; P=0.001) (29).

A similar and controversial image is given by the two other studies which adjusted their results for exclusive cannabis use.

In the retrospective cohort study by Conner et al. a total of 8238 women were included, whereof 680 (8.4%) consumed cannabis during pregnancy. In order to assess the neonatal morbidity the following variables were evaluated: birth weight less than 2500 g, NICU admission, 5-minute Apgar score less than 7 and umbilical artery pH less than 7.10 (30).

The composite of neonatal morbidity was found in 11.6% of women who used cannabis compared to 8.0% of women who did not. After adjusting for confounding factors (i.e. smoking tobacco, other drug use and African American origin) the neonatal outcome of the composite was not significantly (P=0.10) different (30).

In summary, the study situation is controversial. Nevertheless, it seems that concomitant cannabis and tabacco use have an overall negative effect on the newborn.

3.2.5 Effects on the endocannabinoid system and central nervous system

First, the study of Tortoriello et al. hypothesised that THC acts as a “functional antagonist” in developing neurons, since it can displace bindings of high-efficacy endocannabinoids by dampening their signalling efficacy. The authors could show the molecular effects of THC-activated cannabinoid receptors in gravid mice which got intraperitoneally administered 3 mg of THC per kg of body weight. By sampling the diameter of corticofugal axons they discovered an “increased diameter of first-order fascicles relative to vehicle controls” (49).

Second, in another study of Calvigioni et al. was reported that a destabilisation of “tuned signalling networks in altered brain circuit formations” had occurred after intrauterine cannabis exposure (50). In knockout mouse models it was suggested that the signalling is inhibited by several phenotypes (50).

Furthermore, pharmacological studies “imply that endocannabinoids are a nexus in the positioning of neurons and wiring brain circuitry” in foetal brain development (49).

Third, Tortoriello et al. could detect a decreased content of the protein stathmin-2 in the cerebral cortex of human foetuses after intrauterine cannabis exposure. Stathmin-2 is a protein which binds to microtubules in the axons of the brain nerve cells and thus influences the nexus of nerve cells between each other. The researchers suggested that THC may displace endocannabinoids from their receptors on developing neurons. Thus, the originally intended signalling would not have an effect, which ultimately changed the connections between the brain nerve cells (49).

In sum, these studies show the existing evidence for THC-associated brain development disorders on biochemical pathways. There were no existing findings for the early gestational periods, where neuronal induction, proliferation and migration are occurring. Polydrug use is a confounding factor for the last two studies and should be eliminated in future studies. In addition, science should have an eye for the dopamine, opioid, glutamate, and GABAergic neurotransmitter systems and the potential stress-related regions of the brain (e.g. the nucleus accumbens, amygdala, and cortical areas) (15).

3.2.6 Long-term effects

None of the screened reviews reported about a significant adverse neurodevelopmental impact on children after intrauterine cannabis exposure who were two years old or younger.

Lamy et al. have analysed different articles in a retrospective and prospective review and referred to the potential effects of intrauterine cannabis exposure on the long term.

The authors detected a higher probability for several psychomotor troubles. At the age of three years the risk of sleep disorder (after correction of the socioeconomic factors) and of memory disorder were higher. Furthermore, a higher rate of learning disability and attention disorder for children between six and 14 years was observed. It was evaluated using the Wechsler Individual Achievement Test. At age group between four and 14-year-olds, the executive functions, such as planning work and task managing was worse than the average (51).

After all, a higher rate of anxiety disorder, depression, addiction and delinquency was noticeable between ten and 14 years of age. It is to conclude that this study contains many references for different potential effects, however confounding factors were eliminated only for sleep disorder (51).

Warner et al. reviewed 3 different long-term studies of adverse effects on verbal skills, attention, executive and memory functions of three to six years-old children. At ten years of age these children showed difficulties with hyperactivity, impulsivity and inattention (19).

For children in early childhood and school age Jaques et al. reported about slower skill in visual-perceptual tasks and language abilities for cannabis-exposed children (18).

In addition, they analysed timing and the degree of the intrauterine exposure. Thereby they found out that a “heavy use during the first trimester was associated with lower verbal reasoning scores” at six years, while cannabis use during the second trimester “was associated with deficits of composite, short-term memory and quantitative scores” (18).

None of the studies reported about calculated odds values for adverse neuro-developmental outcomes after cannabis exposure in utero.

3.2.7 Maternal cannabis use while breastfeeding

Jaques et al. suggest an eight times higher THC concentration in the human milk in comparison to the simultaneously measured maternal blood plasma concentration after maternal cannabis use. Considering the high concentration of

THC in breast milk of mothers with a relevant cannabis use, it is expected that this practice may have an impact on the nursing baby (18).

The number of studies of human cohorts relating to this topic is poor. The review of Mourh et al. analysed one study where 68 women who continued to use cannabis during lactation compared to 68 women who stopped after pregnancy. The result was that infants with higher cannabis exposure in the first trimester had notably lower psychomotor development index scores (Bayley Infant Scale) compared with infants without being exposured during this period at one year of age. Otherwise, the "neurobehavioural development did not seem to be affected" for the same group (22).

The survey of Bergeria et al. interviewed 120 attendees of the Vermont Lactation Consultant Association conference. 61 of the participants who completed the survey, worked with women who used cannabis during lactation. 44% of them were recommending on a case-by-case basis, 41% recommended to continue lactation in general and only 15% routinely discouraged cannabis users in lactation. This survey indicates that the recommendations for this topic are not consistent and research still remains to be continued (52).

After all, Mourh et al. come to the conclusion that "a conservative approach is suggested until evidence can strongly support otherwise". In sum, those researchers recommend that mothers should be advised to stop recreational use and change medical use to alternative therapies with safe data during lactation (22).

3.2.8 Positive impact on offspring

During the entire literature-searching process only a single study was found, which mentioned positive effects on the newborn after intrauterine cannabis exposure. The research group led by Dreher et al. was investigating cannabis use in Jamaica since the 1960s. They assumed that this country would be suitable for research on cannabis because of less polydrug use as confounding factor at the local population (53).

But due to Rastafarianism and rural structures the drug using patterns are very different to the Western world. First of all cannabis is often drunk for medical reasons in teas by all age groups, children included. In the Rastafarian population traditionally women used to drink and men used to smoke cannabis. This habit changed in the last decades and the number of cannabis-smoking women is increasing. Furthermore, in the poorer rural population groups other drug use (alcohol and tobacco) was quite uncommon in this period (53).

In the study from 1994 Dreher et al. analysed 60 pregnant women concerning their behaviour using cannabis and later on their newborns with the NBAS. The women were split in two matching groups, i.e. exposed and non-exposed. The exposed group was split again in three almost equal categories: “light”, “moderate” and “heavy” users (53).

There was no significant difference between the two groups concerning Apgar scores and clinical examination, including birth weight, length and gestational age at the first day of life. The neurobehavioural outcome was examined with NBAS and had no significantly difference comparing the heavily exposed and nonexposed group (53).

One month after birth NBAS was assessed again and the exposed group showed a significantly better score “on the Autonomic and Reflex clusters of the NBAS”. In addition, the newborns were less irritable and scored higher on the General Irritability item (48).

Furthermore, heavily exposed newborns had significantly higher scores on orientation, autonomic stability and reflexes at NBAS or rather higher individual item scores for ‘habituation to auditory, tactile stimuli and animate auditory stimuli, to the degree of alertness, capacity for consolability, irritability and had fewer startles and tremors’, compared to non-exposed newborns (53).

3.2.9 Cannabis-associated NAS

The “state-of-the-art” article of Jaques et al. reports that newborn withdrawal symptoms “have not been described with exclusive gestational cannabis exposure". However, "subtle neuro-behavioural disturbances such as exaggerated and prolonged startle reflexes and increased hand-mouth behaviour" or rather high-pitched cries and EEG-diagnosed sleep cycle disturbances, have been described. In addition, the researchers refer that there is no need for pharmacological treatment after exclusive cannabis exposure for the neonatological period (18).

In the study of Fried et al. (see subsection 3.2.3) the researchers recognise that serious withdrawal is uncommon but mild symptoms were similar to an opioid-associated withdrawal. They report on significant "Prechtl variables" (Spearman Correlation Coefficients) for increased tremors (Moro tremor: $P<0.01$, and general tremor incidence: $P<0.05$), startles ($P < 0.01$), hand-to-mouth activity ($P<0.01$) and Babinski reflex ($P<0.01$) or rather poorer habituation of visual stimuli. Furthermore, the Prechtl variables relating to muscle strength, i.e. for forearm recoil ($P < 0.05$), elbow resistance ($P<0.01$) and knee resistance ($P<0.05$) were decreased significantly. It should be mentioned that those newborns were examined at day nine and 30 of life and the results showed a similar outcome on both dates. Nevertheless, reflexes posed to be an exception being more pronounced at day 30 of life (47).

3.2.10 Sudden infant death syndrome

There are many studies which showed that maternal drug use is linked to a higher risk of sudden infant death syndrome (SIDS). The case-control study of Klonoff-Cohen et al. was the first research about the correlation of maternal cannabis use or rather paternal drug use in general and SIDS. 478 couples (n=239 cases, n=239 controls) were analysed after their drug use during conception, pregnancy and postnatally. For maternal cannabis use the researchers did not find any significance for all the three periods. Surprisingly, for paternal cannabis use a significant correlation was found during conception (OR 2.2, $P=0.01$), during pregnancy (OR 2.1, $P=0.05$) and postnatally (OR 2.8, $P=0.04$) after adjusting the ORs (54).

4. Discussion

The objectives of this thesis were, firstly, to analyse and evaluate data for the Division of Neonatology of LKH Graz (Austria) and, secondly, to investigate the established knowledge regarding exclusive cannabis use during pregnancy and breastfeeding and its impacts on newborns. Furthermore, the impact on GMs will be discussed.

During the process of the literature search, it became apparent that bibliography reading this matter is rich and that many scientific studies are published. The issue is that many researchers included patients with a concomitant single and polydrug use. In conclusion, other confounding factors, such as varying socioeconomic status, ethnic origin, psycho-social and family-related factors, potentially biased the results. Moreover, the facts that a lot of studies had a small sample size and a retrospective or case-control study design are taken into consideration.

4.1 Summary of results

The adverse impacts on the newborn range from a manifest NAS up to decreased growth chart parameters as well as adverse long-term effects.

In order to give a summarised illustration of the case reports and to draw a conclusion of the searched literature results, the following parameters of perinatal outcome will be considered: birth weight, head circumference, gestational age and number of NICU admissions. Furthermore, long-term effects, co-morbidities and prognosis will be discussed.

4.1.1 Birth weight

One of five newborns in the case reports was born as SGA or rather LBW (normally at least 10 % of all newborns). On average, the birth weight of all five newborns was 2865 g with a decrease of 463 g and a gestational age of 38+6 weeks.

According to the results of literature search, birth weight was the most commonly investigated parameter. It was observed from different perspectives (e.g. absolute birth weight, SGA, LBW, IUGR). The most significant effect of birth-weight associated parameters was reported for an SGA. An approximately three times higher probability or significantly increased odds for SGA were found (10,43).

The second study reported higher odds for LBW and a loss of approximately 110 g for absolute birth weight (43).

Concerning the absolute birth weight, one study mentioned a mean decrease of 272 g (44).

4.1.2 Head circumference

The average head circumference of all case reports was 33.4 cm and had a mean decrease of 1.6 cm.

In view of the literature, a decrease of 0.31 cm (pMD) was reported in the mentioned meta-analysis (43).

Another study, which investigated decreased head circumferences could only find a significance for concomitant tobacco use (29).

4.1.3 Spontaneous preterm birth and neonatal intensive care unit admissions

Considering the case reports, there was neither a case of SPTB nor a case of NICU admission.

One review calculated an increase by the factor of 1.29 (pOR) and another study referred seven times higher odds for an SPTB after intrauterine cannabis exposition (10,43).

The review reported a 2.02 (pOR) higher chance for a NICU admission (43).

4.1.4 Association with GMs

Considering withdrawal symptoms following intrauterine cannabis exposure, we assume that they have influenced the GMs in the writhing period. In our study, GMs were scored "poor repertoire" during the writhing period in two infants. At three months of age, GMs normalised in one infant. From the other infant, no video and consequently no GMA exists.

Our assumption is further supported by the fact that Fried et al. also found poorer scores for infants exposed to cannabis in utero (47). Furthermore, Palchik et al. reported of abnormal GMs in 77 infants with intrauterine opiate exposure (31). Even if there was an important confounding factor of HIV-infection a link to intrauterine cannabis exposure could be expected.

4.1.5 Long-term effects

With regard to long-term effects, it was difficult to paint a picture within our case reports because it was only possible to assess one of all five newborns at the followup. Nevertheless, it is to assume that there could be an adverse impact on long term, not only due to the maternal cannabis use. For example, the difficult social situation, emphasised by the fact that in total four of five newborns of the cases are living in foster families.

This was different in the literature search, where several indications for long-term effects such as troubles in sleep, attention and memory as well as hyperactivity, learning ability and anxiety were found. Furthermore, executive functions, language and visual-perceptual abilities showed adverse outcomes. The rates for addictions, delinquency and depression were higher.

Only one study reported positive effects for children living at the rural side of Jamaica. This study was conducted from the 1960s until 1980s and is not compatible with the conditions of Western countries.

4.1.6 Co-morbidities and prognosis

For one case, a followup including a GMA was achieved, which was completely inconspicuous. There were no other known co-morbidities.

The mentioned adverse perinatal outcomes are linked to each other and are generally associated with a higher risk for the following co-morbidities: neonatal hypoglycaemia or hypocalcaemia, SIDS, cerebral damages (e.g. palsy or movement disorders) and metabolic syndrome in adulthood. An SPTB is especially linked to epilepsy, chronic kidney diseases and depression.

As a result of these findings, we can conclude that maternal cannabis use leads to higher neonatal complications, health impairments, child mortality and healthcare costs.

4.1.7 Dose-effect-relation

Concerning the dose-effect-relation, the link between intrauterine cannabis exposure due to the period of use and SPTB was reported in the study of Leemaqz et al.. They mention a fourfold higher risk of early SPTB and eightfold risk for very early SPTB when cannabis use after the 20^{th} week of gestation (see subsection 3.2.1). The question that arises is if a higher dose of cannabinoids and a longer time of exposition can lead to more significant adverse effects, for example, a higher possibility to develop an NAS (10).

4.2 Limitations

Regarding the limitations, the concomitant drug use and the method of screening should be taken into consideration.

First of all, between 50% and 74% of the pregnant women are using tobacco concurrently. Nevertheless, to exclude further concomitant drug use, there is a difficulty of evaluation and a dependency on the method of screening (18).

Almost 45% of the researchers detected the women by self-report (eight of 18 studies). For self-report, the sensitivity ranges from 0.58 to 0.82 (46), One survey mentioned the limitation for untraceable users. They probably were the heaviest users and could not be included in the study because of ascertainment bias (54).

Drug screening after birth can indicate cannabis, which was used during the second and third trimester, by collecting meconium of the first two days or by sampling the umbilical cord homogenate. In the reality, this is difficult because of the high costs of this screening methods. But relating to the current state of the art, it is not suitable to detect cannabis for the first trimester after pregnancy (18,42).

For potential long-term effects, it is to conclude that it is more difficult to identify them because of their multi-factorial etiology.

4.3 Conclusion

Overall, the birth weight and head circumference values of the case reports, are closer to the lower bound of the normal range (approximately 10th percentile). One case was born as SGA or rather LBW and in total, the social situation is noticeablely difficult. This leads to the conclusion that most of the adverse effects reported in the literature could been also observed in the case reports.

After summarising the results of literature search and case reports, it is to conclude that cannabis use during pregnancy can adversly affect newborns on many levels or ways, especially concerning birth weight, gestational age and head circumference.

The following citation of the meta-analysis of Gunn et al. illustrates the central questions about this subject matter.

“As use of cannabis gains social [and medical] acceptance, pregnant women and their medical providers could benefit from health education on potential adverse effects of use of cannabis during pregnancy” (43).

The change in drug policy in several Western countries has led to a decriminalisation and legalisation of recreational and medical cannabis. This trend probably will further cause an increase of drug use during preagnacy and the reported consequences. Taking into account that social acceptance is linked to the rising trend of medical cannabis use and the opening for to a public discussion.

4.4 Outlook

It should be noted that the estimation was based on the initial proportion of 0,5% women who have a high-risk use of cannabis. Other studies report a substantial higher proportion (see below).

After expecting four cases yearly at the Graz location, it must also be acknowledged that a big part of cannabis users have an accompanied use of tobacco, opiates, stimulants and alcohol (subsections 3.2.4) Especially the high-risk users, who continue consuming during pregnancy (17).

It was not possible to calculate a number of cases after exclusive intrauterine cannabis exposure. Furthermore, it is to assume that the estimated number of unreported cases is far higher.

Concerning the proportion of pregnant women who consumed cannabis in Western countries, different numbers were found. For the U.S. they range from 4% (46), up to 5,2% (19) as well as 20% (13) and for the part of Great Britain, Australia and New Zealand 5.6 % (10) was reported. Furthermore, the range for industrial countries was generally indicated with 2-13% (44) and 2-11% (29).

The prevalence numbers are depending "of the populations studied and the mode of detections" (30). This citation from Conner et al. illustrates the variability of prevalence reported in the literature.

After this consideration, it would be more realistic to start with a tenfold higher initial value. This leads us to the conclusion that the prevalence of this topic will be higher. This point underpins the relevance and shows the need to provide more research in this field of study.

In order to work on prevention, more education and information at schools and social hot spots should take place. Especially, if we consider the possibility of further legalisation of medical and recreational cannabis and the social acceptance that this substance will gain in Austria and other European countries.

Maternal cannabis use was the primary focus of this thesis, but we should not neglect the role of paternal cannabis use during pregnancy and infancy. Taking into consideration the fact that often there are existing co-dependencies in couples which are further associated with violence, poverty and low socioeconomic status, it is to assume that paternal drug use can play a crucial role for neonatal outcomes.

5. Bibliography

1. Kocherlakota P. Neonatal Abstinence Syndrome. Pediatrics. 2014;134(2):e547–61.
2. Liu G, Kong L, Leslie DL, Corr TE. A Longitudinal Healthcare Use Profile of Children with a History of Neonatal Abstinence Syndrome. J Pediatr. 2018;8(32):1–8.
3. Witt CE, Rudd KE, Bhatraju P, Rivara FP, Hawes SE, Weiss NS. Neonatal abstinence syndrome and early childhood morbidity and mortality in Washington state: A retrospective cohort study. J Perinatol. 2017;37(10):1124–9.
4. Prechtl HF, Einspieler C, Cioni G, Bos AF, Ferrari F, Sontheimer D. An early marker for neurological deficits after perinatal brain lesions. Lancet. 1997;349(9062):1361–3.
5. Ploegstra WM, Bos AF, de Vries NKS. General movements in healthy full term infants during the first week after birth. Early Hum Dev. 2014;90(1):55–60.
6. Einspieler C, Marschik PB, Pansy J, Scheuchenegger A, Krieber M, Yang H, et al. The general movement optimality score: A detailed assessment of general movements during preterm and term age. Dev Med Child Neurol. 2016;58(4):361–8.
7. Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. JAMA Pediatr. 2017;171:897–907.
8. European Monitoring Centre for Drugs and Drug Addiction (2017), European Drug Report 2017: Trend and Developments, Publications Office of the European Union, Luxembourg. 2017;1–90.

9. Weigl, Marion; Anzenberger, Judith; Grabenhofer-Eggerth, Alexander; Horvath, Ilonka; Schmutterer, Irene; Strizek, Julian; Tanios A (2017): Bericht zur Drogensituation 2017. Gesundheit Österreich, Wien. 2017.

10. Leemaqz SY, Dekker GA, McCowan LM, Kenny LC, Myers JE, Simpson NAB, et al. Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications. Reprod Toxicol. 2016;62:77–86.

11. LKH-Univ. Klinikum Graz. LKH-Univ. Klinikum Graz - Kennzahlen 2017. 2017.

12. Informationen S. Familien in Zahlen 2017. 2017;43(0):1–101.

13. Martin CE, Longinaker N, Mark K, Chisolm MS, Terplan M. Recent Trends in Treatment Admissions for Marijuana Use During Pregnancy. J Addict Med. 2015;9(2):99–104.

14. Dr. Kurosch Yazdi. Die Cannabis-Lüge. Schwarzkopf & Schwarzkopf Verlag GmbH, editor. Berlin; 2017. 255 p.

15. M. L, Jansson M. Perinatal Marijuana Use and the Developing Child. JAMA. 2017;320(6):545–6.

16. Eckardstein MSMGA von. Biochemie und Molekularbiologie des Menschen. München: Elsevier Ltd; 2013. 1056 p.

17. Hindocha C, Freeman TP, Ferris JA, Lynskey MT, Winstock AR. No smoke without tobacco: A global overview of cannabis and tobacco routes of administration and their association with intention to quit. Front Psychiatry. 2016;7(JUL):1–9.

18. Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, et al. Cannabis, the pregnant woman and her child: Weeding out the myths. J Perinatol. 2014;34(6):417–24.

19. Warner TD, Roussos-Ross D, Behnke M. It's not your mother's marijuana: Effects on maternal-fetal health and the developing child. Clin Perinatol. 2014;41(4):877–94.

20. Campolongo P, Trezza V, Ratano P, Palmery M, Cuomo V. Developmental consequences of perinatal cannabis exposure: Behavioral and neuroendocrine effects in adult rodents. Psychopharmacology (Berl). 2011;214(1):5–15.

21. Fride E, Gobshtis N, Dahan H, Weller A, Giuffrida A, Ben-Shabat S. Chapter 6 The Endocannabinoid System During Development: Emphasis on Perinatal Events and Delayed Effects. 1st ed. Vol. 81, Vitamins and Hormones. Elsevier Inc.; 2009. 139-158 p.

22. Mourh J, Rowe H. Marijuana and Breastfeeding: Applicability of the Current Literature to Clinical Practice. Breastfeed Med. 2017;12(10):582–96.

23. § 27 SMG Unerlaubter Umgang mit Suchtgiften [Internet]. Suchtmittelgesetz, SMG -. 2018 [cited 2018 Aug 23]. Available from: https://www.jusline.at/gesetz/smg/paragraf/27

24. 689 der Beilagen zu den Stenographischen Protokollen des Nationalrates XXV. GP. In 2016. p. 1–23.

25. United Nations Office on Drugs and Crime. World Drug Report 2017. United Nations Publ. 2017;1–66.

26. Weigl, Marion; Anzenberger, Judith; Busch, Martin; Grabenhofer-Eggerth, Alexander; Horvath, Ilonka; Schmutterer, Irene; Strizek, Julian; Türscherl E. Bericht zur Drogensituation 2016.Gesundheit Österreich, Wien. 2016.

27. Laqueur H. Uses and Abuses of Drug Decriminalization in Portugal. Law Soc Inq J Am Bar Found. 2014;40(3):746–81.

28. Der Fischer Weltalmanach 2017. Frankfurt am Main, S Fischer Verlag GmbH. 2016;736.

29. Chabarria KC, Racusin DA, Antony KM, Kahr M, Suter MA, Mastrobattista JM, et al. Marijuana use and its effects in pregnancy. Am J Obstet Gynecol. 2016;215(4):506.e1-506.e7.

30. Conner SN, Carter EB, Tuuli MG et al. Maternal marijuana use and neonatal morbidity. Am J Obstet Gynecol. 2015;213(422):1–4.

31. Palchik AB, Einspieler C, Evstafeyeva I V., Talisa VB, Marschik PB. Intra-uterine exposure to maternal opiate abuse and HIV: The impact on the developing nervous system. Early Hum Dev. 2013;89(4):229–35.

32. Irwin OC WA. A note on mass activity innewborn infants. Pedagog Semin. 1930;38:20–9.

33. Prechtl HFR, Fargel JW, Weinmann HM, Bakker HH. Postures, Motility and Respiration of Low-risk Pre-term Infants. Dev Med Child Neurol. 1979;21(1):3–27.

34. Prechtl HFR. Qualitative changes of spontaneous movements in fetus and preterm infant are a marker of neurological dysfunction. Early Hum Dev. 1990;23(3):151–8.

35. Prechtl HFR. Ultrasound studies of the human fetal behaviour. Early Hum Dev. 1985;(12):91–8.

36. Einspieler C, Prechtl H, Bos A, Ferrari F CG. Prechtl´s Method on the Qualitative Assessment of General Movements in Preterm, Term and Young Infants. London: Mac Keith Press. 2004. 104 p.

37. de Vries JIP, Visser GHA PH. The emergence of fetal behaviour. I. Qualitative aspects. Early Hum Dev . 1982;7:301–22.

38. Calvigioni D, Hurd YL, Harkany T, Keimpema E. Neuronal substrates and functional consequences of prenatal cannabis exposure. Eur Child Adolesc Psychiatry. 2014;23(10):931–41. motor behaviour in low-risk premature infants. Early Hum Dev. 1990;23(3):159–91.

39. Hopkins B PH. A qualitative approach to the development of movement during early infancy. In: Continuity of the neural functions from prenatal to postnatal life. H.F.R. Prechtl. Blackwell O, editor. Vol. 94, Clinics in Developmental Medicine. Oxford, UK; 1984. 179-197 p.

40. Ferrari F, Cioni G, Prechtl HFR. Qualitative changes of general movements in preterm infants with brain lesions. Early Hum Dev. 1990;23(3):193–231.

41. Gomez-Pomar E, Finnegan LP. The Epidemic of Neonatal Abstinence Syndrome, Historical References of Its' Origins, Assessment, and Management. Front Pediatr. 2018;6(February):1–8.

42. Metz TD, Allshouse AA, Hogue CJ, Goldenberg RL, Dudley DJ, Varner MW, et al. Maternal marijuana use, adverse pregnancy outcomes, and neonatal morbidity. Am J Obstet Gynecol. 2017;217(4):478–478.

43. Gunn JKL, Rosales CB, Center KE, Nuñez A, Gibson SJ, Christ C, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. BMJ Open. 2016;6(4):1–8.

44. El Marroun H, Tiemeier H, Franken IHA, Jaddoe VWV, van der Lugt A, Verhulst FC, et al. Prenatal Cannabis and Tobacco Exposure in Relation to Brain Morphology: A Prospective Neuroimaging Study in Young Children. Biol Psychiatry. 2016;79(12):971–9.

45. Minnes S, Lang A, Singer L. Prenatal Tobacco, Marijuana, Stimulant, and Opiate Exposure: Outcomes and Practice Implications. Addict Sci Clin Pr. 2011;6(1):57–70.

46. van Gelder MMHJ, Donders ART, Devine O, Roeleveld N, Reefhuis J. Using Bayesian Models to Assess the Effects of Under-reporting of Cannabis Use on the Association with Birth Defects, National Birth Defects Prevention Study, 1997-2005. Paediatr Perinat Epidemiol. 2014;28(5):424–33.

47. Fried PA, Watkinson B, Dillon RF et al. Neonatal neurological status in a low-risk population after prenatal exposure to cigarettes, marijuana, and alcohol. J Dev Behav Pediatr; 1987. p. 9.

48. Hayes JS, Lampart R, Dreher MC et al. Five-year follow-up of rural Jamaican children whose mothers used marijuana during pregnancy. West Indian Med J. 1991;40(120):123.

49. Tortoriello G, Morris C V, Alpar A, Fuzik J, Shirran SL, Calvigioni D, et al. Miswiring the brain: D 9 -tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. EMBO J. 2014;33:668–85.

50. Calvigioni D, Hurd YL, Harkany T, Keimpema E. Neuronal substrates and functional consequences of prenatal cannabis exposure. Eur Child Adolesc Psychiatry. 2014;23(10):931–41.

51. Lamy S, Laqueille X, Thibaut F. Conséquences potentielles de la consommation de tabac, de cannabis et de cocaïne par la femme enceinte sur la grossesse, le nouveau-né et l'enfant: revue de littérature. Encephale. 2015;41(S1):S28–35.

52. Bergeria CL, Heil SH. Surveying Lactation Professionals Regarding Marijuana Use and Breastfeeding. 2015;10(7):377–80.

53. Dreher MC, Nugent K, Hudgins R. Prenatal Marijuana Exposure and Neonatal Outcomes in Jamaica: An Ethnographic Study. Pediatrics. 1994;93(2):254–60.

54. Klonoff-Cohen H, Lam-Kruglick P. Maternal and paternal recreational drug use and sudden infant death syndrome. Arch Pediatr Adolesc Med. 2001;155(7):765–70.

6. Attachment

6.1 Figure 6:

Finnegan Score used at the Division of Neonatology at LKH Graz

Klinisches Kriterium	1 Punkt	2 Punkte	3 Punkte	4 Punkte	5 Punkte
Schreien		Häufig	Ständig		
Schlafen n. Füttern	3 Std.				
Myoklonie in Ruhe			Ja		
Myoklonie bei Störung		Ja			
Muskeltonus		Erhöht			
Hautabschürfungen	Ja				
Krämpfe					Ja
Schwitzen in Ruhe		Ja			
Temperatur instabil		Ja			
marmorierte Haut	Ja				
Gähnen	Ja				
Verstopfte Nase		Ja			
Niesen	Ja				
Atmung	über 60/min.				
Starkes Saugen		Leicht	Stark		
Trinkschwäche		Ja			
Erbrechen		Leicht			Im Guss
Stuhlkonsistenz			Dünn	Wässrig	
Stuhlhäufigkeit	5 mal	6 mal	7 mal	8 mal	9 mal
Gesäß	Gerötet	Wund	Offen		
Blähungen		Leicht	Stark		
Datum:				Punkte:	

6.2 Appendix – Search

1. MEDLINE, search surface: PubMed, 17/10/2017

Search #1: “Marijuana”	25416
Search #2: "Cannabis"	17234
Search #3: “Pregnancy”	917548
Search #4: “General Movements”	36916
Search #5: “Breastfeeding”	49304
Search #6: “Neonatal abstinence syndrome”	1196
Search #7: “Finnegan Score”	84
Search #8: “THC”	9121
Search #9: (#1 OR #2) AND #3	1246
Search #10: (#1 OR #2) AND #4	37
Search #11: (#1 OR #2) AND #5	58
Search #12: (#1 OR #2) AND #6	42
Search #13: #5 AND #8	12
Search #14: #6 AND #8	3

2. Cochrane Library, 08/10/2017

Search #1: “Pregnancy marijuana”	28
Search #2: "Pregnancy, Cannabis"	26
Search #3: “Breastfeeding, Cannabis”	37
Search #4: “Neonatal abstinence syndrome”	5
Search #5: “General Movements”	245
Search #6: “Finnegan Score”	25