COVID-19 and Zika-infections during pregnancy

Effects on the pregnant woman, the placenta and her offspring

Maria Emilie Duesund

Supervisor: Prof. Anne Cathrine Staff

Project thesis, Faculty of Medicine

University of Oslo

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I Introduction

Pregnant women are usually not more exposed to viral infections than the non-pregnant population. Some infectious diseases are nevertheless more serious in pregnancy, due to the pregnancy's unique physiological and immunological state (1). In addition, a pregnancy involves more than one individual, namely both a woman (the mother-to-be) and at least one offspring.

Whereas the effect of the Zika virus (ZIKV) on the fetus is relatively well understood, knowledge on how SARS-CoV-2 infections would affect the pregnant women and the fetus was unknown at the start of the COVID-19 pandemic situation in early 2020. There have been many concerns worldwide on COVID-19's effect on pregnant women, ever since the World Health Organization declared the Corona virus a Public Health Emergency of international concern in 2022 (2). From the beginning it seemed that there was little risk for the fetus being affected unless the pregnant woman herself was severely clinically affected by COVID-19. This contrasts with ZIKV infection, where an asymptomatic mother may give birth to a child with severe birth defects.

The objectives of this project thesis were therefore to review and compare relevant literature regarding pregnancy affected by Zika or COVID-19, including assessing effects on the pregnant woman, the placenta and neonates following infection with SARS-CoV-2 and ZIKV during pregnancy. The project thesis aims to investigate conditions in Norway, but the global situation is also discussed. The thesis is written as a part of the medical student program at the Medical Faculty, University of Oslo.

My supervisor Professor Anne Cathrine Staff, Oslo University Hospital and University of Oslo, has given me brilliant supervision while working with this thesis. Her guidance and advice as well as enthusiasm and support has been greatly valued.

II Abstract

Objectives: The objective of this project thesis is to determine the clinical manifestations, risk factors, and maternal and perinatal outcomes in pregnant women with confirmed or suspected SARS-CoV-2, and to compare these findings to the Zika virus epidemic during 2015/2016, that has provided well-known knowledge about fetal risks.

Methods: The project thesis is based on a non-systematic literature review. Relevant search terms were used in different combinations in PubMed, identifying relevant research findings to compare these epidemics and how they affect pregnant women and their offspring. Background information about the maternal immune system, placental physiology as well as the two infections' epidemiology were also obtained and considered.

Results: There is clear evidence of a significant risk of fetal transmission and thereby possible adverse and severe offspring outcomes following maternal Zika infection. However, a direct viral maternal-fetal transmission mechanism is not found with COVID-19. With COVID-19 infection, the maternal and fetal outcomes seem to heavily rely on the maternal health prior to the infection, including COVID-19 vaccination status.

Conclusions: There are still challenges regarding the prevention, diagnostics and treatment of both ZIKV and SARS-CoV-2 infections. Long-term effects are still unknown, nevertheless the fetal effects of Zika are better understood. Severe adverse maternal and fetal outcomes after maternal COVID-19 infections seem to be preventable by vaccination, however more research is needed for a better understanding of the long-term COVID-19 effects.

III Background

COVID-19 and Zika infections have affected large populations even though the epidemiologies of the viruses differ. The epidemic of ZIKV disease in 2015-2016 may share some similarities to the ongoing pandemic of COVID-19, in that infection of pregnant women may lead to adverse pregnancy outcomes. The Zika virus may severely affect the fetus, but the epidemic only affected pregnancies in limited areas of the world. In the beginning of the COVID-19 pandemic, in March 2020, it was uncertain whether pregnant women were at the same risk of being infected by COVID-19 as non-pregnant fertile persons. Although vertical transmission to the fetus did not seem to occur in the same way as in ZIKV disease, it was not known if pregnant women were at higher risk of severe disease. Later during the COVID-19 pandemic, when the vaccine became generally available at the start of 2021, there was no knowledge as to whether it was safe to offer pregnant women vaccination, and whether vaccination in some trimesters in pregnancy should be avoided.

The Zika virus was first discovered in 1947 and is named after the Zika Forest in Uganda. The first cases of Zika infections in humans were detected in Uganda and Tanzania in 1952. Later on, outbreaks of Zika have occurred in many locations, not all being reported (3). From the 60s to 80s Zika expanded to Asia where the virus was detected in mosquitos (4). In 2015 and 2016 there was a significant spread of the ZIKV in South and Central America, as well as in the southern parts of the United States. Up until this point ZIKV was considered a benign virus, even though there was observed a rapid increase in neonates born with microencephaly. This led to the discovery of ZIKV-induced congenital abnormalities including microencephaly, intrauterine growth restriction and eye disease that can result in blindness, also known as the Congenital Zika Syndrome (CZS). On the 11th of November 2015, the Brazilian Ministry of Health declared the possible association between ZIKV infection in pregnancy and offspring microencephaly (5). Studies have shown that ZIKV crosses the placenta and replicates within fetal tissues including the developing brain (6). Most antenatally infected fetuses do however not develop microencephaly.

In late 2019, a new pandemic started rapidly to spread across the world, causing severe illness and deaths for many. Coronavirus disease (COVID-19) was first reported by the World Health Organization (WHO) in December 2019, after a cluster of cases with unknown pneumonia in Wuhan, China (7). In the afternoon of March 11th 2020 WHO declared

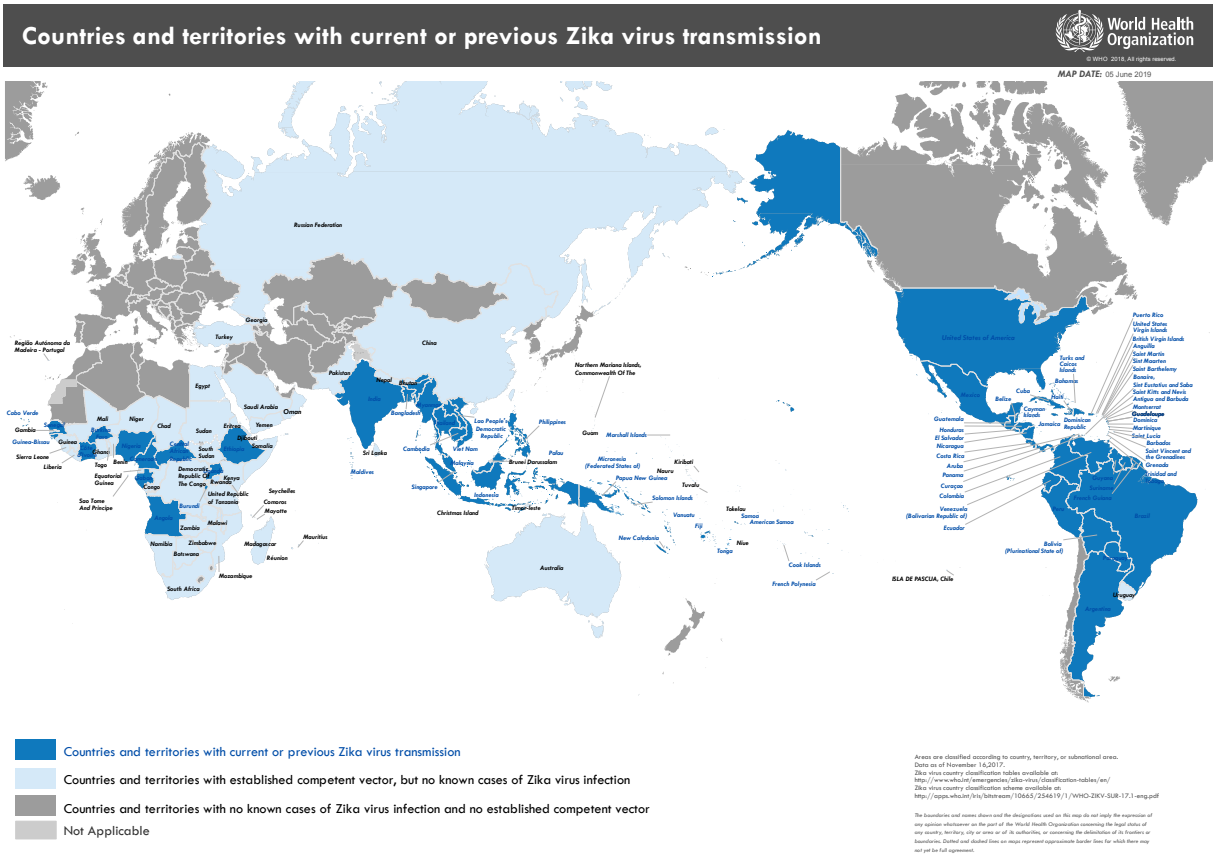
COVID-19 a pandemic (2) . The COVID-19 pandemic has, by 25th of January 2022, led to over 5,6 million deaths and 352 796 704 cases of COVID-19 have been reported to the WHO. America and Europe have reported both most cases and deaths (8).

In general, the risk for pregnant women of viral infection or becoming seriously ill, are not higher than for other groups, but some illnesses may become more serious than in non-pregnant persons. This was for example seen in the swine flu pandemic in 2009, caused by the H1N1 influenza virus. Infection with swine flu influenza increased the risk of morbidity, mortality, and pregnancy-related complications (including spontaneous miscarriage and preterm birth) (9).

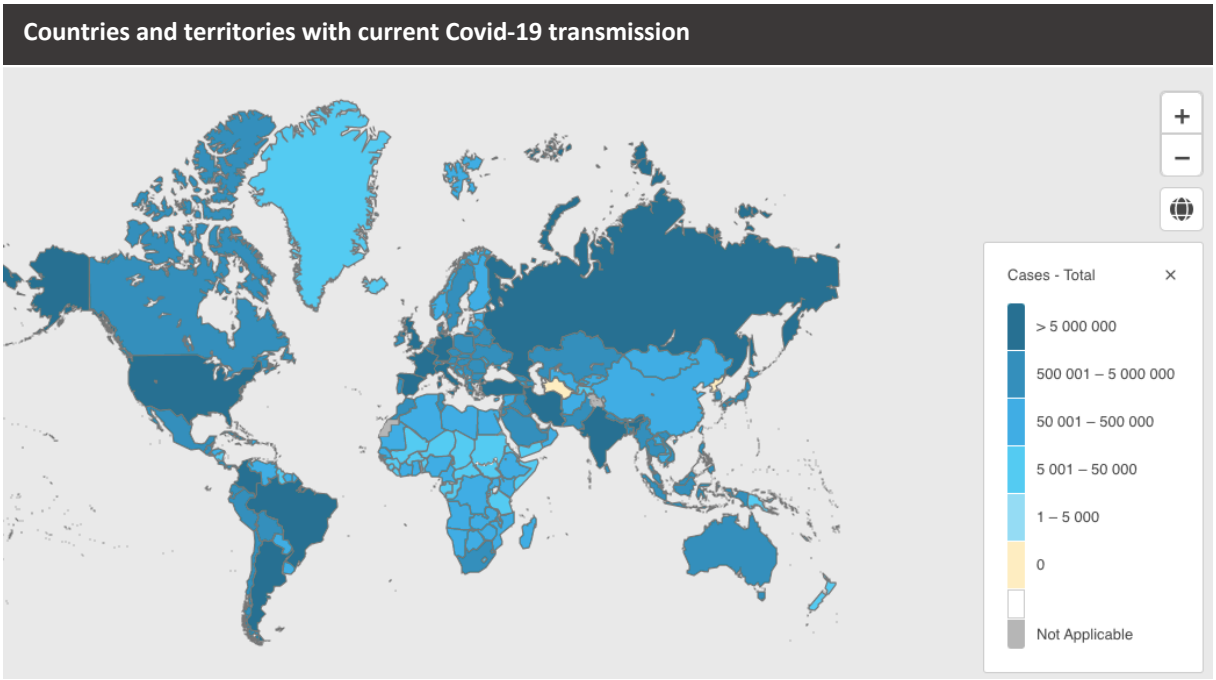
Infections can be transmitted from the mother to the fetus in different ways during pregnancy or during birth. The most vulnerable time of adverse fetal development following an infection is usually during the embryonic period, but can also occur later in the pregnancy causing adverse pregnancy outcome like preterm birth. The consequences of viral infection in pregnancy can be congenital illness for the offspring or chronical infections (1), as well as an adverse pregnancy outcome often affecting both the mother and offspring.

Epidemics, and/or pandemics, are a threat to the general population. Pregnant women are considered as a more vulnerable group, similarly to other parts of the population like children and the elderly, who *might* be at higher risk for severe disease. In the ZIKV epidemic, the hypothesis about the connection to CZS was understood after a great number of causes, likely due to the mothers being asymptomatic. In contrast, the COVID-19 virus pandemic was rapidly acknowledged, but there was no knowledge of how pregnant women or their offspring would be affected in cases of maternal infection.

Maps 1 and 2 from WHO show the occurrence of ZIKV and SARS-CoV-2 worldwide (as of respectively June 2019 and the start of 2022).



Map 1. Source: downloaded from WHO, June 2019 (10).



Map 2. Source: WHO Coronavirus Dashboard Jan 10th 2022 (8).

3.1 The Zika virus - ZIKV

The Zika virus (ZIKV) is a single-stranded RNA arbovirus producing untranslated RNA. ZIKV is a member of the virus family *Flaviviridae* (flavivirus) (11). ZIKV is thought to be involved in an antiviral response in the host, inducing cell death (12). ZIKV infection has similarities with other TORCH classified infections like Rubella, Herpes Simplex Virus and Varicella Zoster Virus. TORCH pathogens can be vertically transmitted from mother to fetus by crossing the placental barrier and possibly lead to congenital defects (13).

ZIKV is present in tropical areas and nearly half of the world's population lives in area with risk of infection (14). After the big epidemic in 2015-2016, the number of infected individuals have been reduced. The last known outbreak was reported by WHO in July, 2021, based on findings in south-west India (15). In Norway there have been very few cases of documented ZIKV infection, and none of these were pregnant women (1).

3.2 The Coronavirus – SARS-CoV-2

The new Corona virus, SARS-CoV-2, causes COVID-19 disease. It belongs to the Corona virus family, causing respiratory infection with a variety of severity (16). Coronaviruses are RNA viruses, entering the host cell through binding of their spike glycoprotein with the cell-surface receptor angiotensin-converting enzyme-2 (ACE2) receptors. Transmembrane protease serine 2 (TMPRSS) has an important role facilitating the cell infection (17). The number of COVID-19 cases increased rapidly worldwide from the start of the 2020 pandemics (18), with a basic reproduction number of 2-2.5 (19). Since the start of the pandemic, the virus has undergone several recognized major mutations, that have changed the infectious pattern and clinical severity. The current pneumonia outbreak due to SARS-Cov-19 is present on all continents and seems to occur in humans of all ages. However, elderly persons and patients with comorbidities more frequently develop severe COVID-19 illness (20).

3.3 Immunological adaptions in pregnancy and possible implications during viral infections

Pregnancy represents an unique immunological condition due to the development of a fetus, and significant adaptations occur in the mother-to-be to stimulate tolerance to the fetus as a semi-allograft. These adaptions involve increased hormone levels and immune cell shift

among other things, and these changes may increase the susceptibility to some infections during pregnancy (21-23).

As fertilization occurs, the levels of maternal hormones like human chronic gonadotropin (hCG) and progesterone rise, and immune tolerance towards the invading trophoblast is established by these hormones promoting an immune suppression. Some adaptive immune responses are down-regulated, especially regulatory T-cells (Treg) and natural killer (NK) cells (24). This change helps inhibiting maternal rejection of the fetus and the placental tissue in the early stages of pregnancy. Pregnant women however are not considered immunosuppressed (22), but rather possessing a modified immune system .

The embryo can be seen as a semi-allograft, comprising paternal and maternal genes, and is sustained by complex mechanisms of maternal-fetal tolerance. The mechanisms of the maternal-fetal interface are already widely investigated, but not completely understood. However, recent findings add mechanisms of the peripheral maternal-fetal crosstalk where this interaction also occurs in maternal circulation, not only at the border of fetal-maternal tissues in the uterine wall. Peripheral maternal immune cells carry fetal antigen, where the concentration is at its highest mid and late stages of pregnancy. However, these fetal antigen-carrying immune cells have a homeostatic cytokine profile in the peripheral maternal circulation (25).

3.4 Placental physiology in pregnancy and possible affection during maternal infections

Placental affection during viral infections may also affect pregnancy outcome and placental transfer. If placental transmission of a virus or bacteria occurs, the infection can lead to adverse fetal outcomes, such as congenital anomalies as well as fetal death or miscarriage. However, the placenta or/and the fetus might also be affected by the mother's infectious response, regardless of vertical transmission of the infectious agents (21). Several viral and bacterial infections are correlated with chorioamnionitis, which again is associated with preterm birth (26) and adverse fetal effects. "*Although viral infections are common during pregnancy, transplacental passage and fetal infection appear to be the exception rather than the rule" (21)*.

The placenta functions as the fetus' supply of oxygen and nutrients during pregnancy, as well as performing the work that separate fetal organs will take over later on. The placenta has a large surface with few placental cells separating the maternal and fetal circulation, facilitating fetal-maternal transport as well as serving as a barrier for protection (27). The barrier and its regulation is important as a normal microenvironment is required for the fetus to develop normally. The multinucleated syncytiotrophoblast layer covering the placental villi, function with a variety of enzymes and transporters which enables detoxification and efflux of molecules. The placenta thereby helps preventing potential harmful exposure for the fetus (27). Cardenas et al (2010) suggest for example how viral infection of the placenta leads to fetal inflammation and sensitization to bacterial products predisposing to preterm labour (28).

3.5 Transmission routes in pregnancy

Maternal-fetal transmission is where pathogens can pass from mother to child either in the womb or during delivery. There are two basic routes for fetal access during pregnancy; the ascending or transvaginal route and the transplacental or haematogenic route (29). In-utero transmission of virus can be either vertical or hematogenous, via the placenta, or ascending via the reproductive tract (22). Ascending infection often involves rupture of the membranes (amniotic sac) and thereby facilitating pathogens to infect the amniotic fluid.

Vertical transmission is often transplacental but can also occur during childbirth, the latter named mother-to-child transmission (22). Transplacental transmission allows microorganisms to enter the placenta through the maternal vessels and cross the placental barrier by villous structures covered in maternal blood (29). Inflammation of the placental villi (villitis) induced by microorganisms causes cellular damage and represents a possible transmission route as well as cell-mediated transport (29).

IV Aims, materials and methods

The objectives of this project thesis were to review and compare relevant literature regarding pregnancy affected by Zika or COVID-19, including assessing effects on the pregnant woman, the placenta and neonates following infection with SARS-CoV-2 and ZIKV during pregnancy. The project thesis aims to investigate conditions in Norway, but the global situation is also discussed.

This project thesis is based on a non-systematic literature review including combinations of different search terms in the PubMed Medline database, performed primarily autumn and winter 2021/2022. The search was last updated Jan 3rd 2022. Two separate literature searches on infection with *either* ZIKV *or* SARS-CoV-2 during pregnancy were performed. In addition, a search combining these findings using an advanced search with combination of the infections was performed. The Medical Library at the University of Oslo was helpful in identifying Mesh terms and supporting the search in PubMed. *Table 1* illustrates the process of identifying the papers providing information for this thesis.

The following terms were used and combined in the search:

(Zika Virus Infection[Mesh] OR zika[Title])
AND (either)
("Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR "Pregnancy Complications"[Mesh] OR pregnant[Title] OR pregnancy[Title] OR pregnancies[Title])

("COVID-19"[Mesh] OR (("corona virus"[Title] OR coronavirus[Title]) AND (Wuhan[Title] OR 2019[Title] OR novel[Title] OR 19[Title])) OR COVID-19[Title] OR COVID19[Title] OR nCoV[Title] OR nCoV19[Title] OR SARS-CoV-2[Title] OR SARS-CoV2[Title] OR severe acute respiratory syndrome coronavirus 2[Title])
AND (either)
("Pregnancy"[Mesh] OR "Pregnant Women"[Mesh] OR "Pregnancy Complications"[Mesh] OR pregnant[Title] OR pregnancy[Title] OR pregnancies[Title])

Filters used: Abstract, review.

Articles from these searches were then selected based on titles and abstract reading in agreement with supervisor, Professor Anne Cathrine Staff. Articles with other main topics than the aim of this project thesis were excluded. Professor Staff has great competence in the placental and obstetric research field and has provided a selection of additional studies and articles of relevance during the work on the project thesis. To provide additional background information, books from the Medical University library and PubMed have been used. National Guidelines like NICE (National Institute for Health and Care Excellence UK) and the Norwegian Guidance in Obstetrics (2020) have also been used for reference literature.

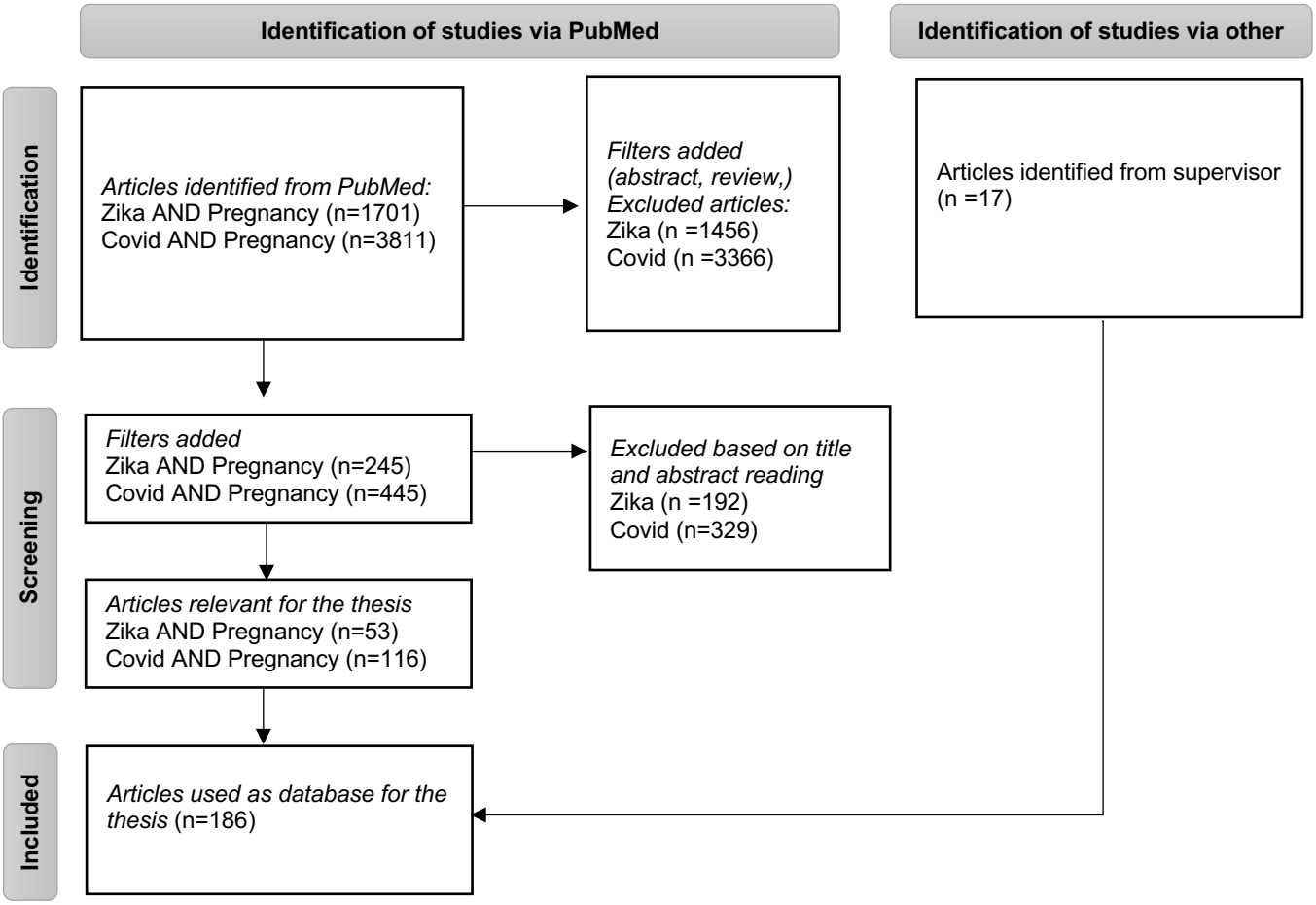


Table 1: Flow diagram illustrating article selection for the project thesis

V Results

5.1 Zika infection during pregnancy

5.1.1 Clinical manifestations

The incubation period of ZIKV is 3-12 days (1). The infection is asymptomatic for most (70-80%), yet some may experience light fever, headache, muscular pain, conjunctivitis, or maculopapular rash (14). Symptoms are often mild and self-limiting and last up to one week. The Guillain-Barré-syndrome is a rare complication to ZIKV and is estimated to occur in 1.2% cases, leading to mortality and significant disability in 5% and 20% respectively (14). ZIKV infection in pregnancy is not associated with more frequent or severe complications for the woman herself (30).

5.1.2 Transmission of virus

The transmission of ZIKV can occur in different ways; vector/mosquito-borne and non-vector-borne/blood-borne; either sexual, by transfusion or materno-fetal (vertical transmission). The Ae. aegypti mosquito is the major vector for ZIKV and it is present in tropical areas. These mosquitoes bite most actively in the daytime but also bite at night (11).

The first estimate of fetal infection was 10.9% based on amniocentesis and serology testing of newborns from French Guiana. When adding fetal/neonatal and placental samples, the estimate was 26.1%. When excluding positive placenta samples, the maternal-fetal transmission rate has been estimated to 18% (30). ZIKV particles have also been detected in breast milk, but lactation has not been seen as a transmission route (14). The fetus can be infected by the virus via the placenta after maternal infection whether the mother experience symptoms or not (1).

Different routes of maternal-fetal transmission of ZIKV have been suggested. An ascending route is not yet proven in humans, but thought to be a possible way of virus reaching the fetus due to sexual contact (31). As the virus can enter the maternal bloodstream from vaginal exposure the virus might enter the transplacental transmission route subsequently (29).

The transplacental route is a consequence of ZIKV from maternal bloodstream to enter terminal villi and Hoffbauer cells (HBCs), as they are the main target cells during ZIKV infection of the placenta. These villi interact with fetal capillaries (32). The TAM receptors

(Tyro3, Axl, MertK) are receptor tyrosine kinases putative for placental entry of ZIKV (33). Both placental villi cells (HBCs) and cells of the placental membranes express TIM1 (T-cell immunoglobulin and mucin 1). TIM1 is a suggested key entry cofactor of the ZIKV and thereby facilitate two suggested routes of maternal-fetal transmission through the placenta, either through placental HBCs or the membranes (34).

The proposed mechanisms for developing CZS is through viral particles in the fetal circulation binding to the AXL receptor, a receptor tyrosine kinase, entering the fetal neuronal progenitor cells. By binding to Toll-like-receptor 3 (TLR3), a receptor-mediated gene regulating in the nucleus is activated, resulting in down-regulated gene expression of 41 genes coding for fetal neuronal development as well as upregulating apoptosis (32). As the fetal central nervous system forms the first eight weeks of pregnancy, the risk of severe TORCH infections and thereby Zika infection decreases after seventeen weeks of gestation (13).

5.1.3 Placental affection

The maternal-fetal ZIKV transmission is driven by the placental inflammation initiating placental macrophages transferring from the placenta to the fetal brain (14). Histopathological findings on ZIKV infected placentas are non-specific, and like other placental infections include chronic placentitis, villitis, increased numbers of placental macrophages, irregular fibrin deposits, increased mononuclear cells in villous stroma, villous immaturity, oedema, hypervascularization, stromal fibrosis, calcifications, and focal necrosis of syncytiotrophoblasts (14, 35). These findings are consistent with other viruses affecting the placenta, leading to a proinflammatory response, where the amount of inflammation is correlated to the fetal outcome severity (35). There has also been reports of possible hypoperfusion in ZIKV affected placentas (14).

5.1.4 Outcomes for the mother and her offspring

When the link between ZIKV infected women and their infants with CZS was suspected, reports suggested a risk of severe fetal anomalies to about 40%. A cohort study from western French Guiana, including 300 participants, estimated the rate of maternal-fetal ZIKV transmission, finding a 25% risk of fetal congenital infection t when there is a known ZIKV infection in the mother. A third of these developed severe complications and the study therefore concluded that the CZS burden might be lower than thought in the beginning. This

also indicates that the rates of maternal fetal transmission is comparable to other congenital viruses (36). The risk of fetal transmission is thereby significant with maternal ZIKV infection.

The outcome for the ZIKV infected mother is described as mild, yet for her offspring infection with ZIKV can lead to neurodevelopmental impairment as well as pregnancy loss. Congenital Zika Syndrome (CZS) includes microencephaly, brain disruption, ocular anomalies and contractures. Seizures are also seen as a consequence to the mentioned brain defects. In utero exposition may lead to microencephaly development and/or later neurodevelopmental impairment (14). Microencephaly is a late but well-known symptom and lesions, calcifications and ventriculomegaly are some of its earlier manifestations.

Secondary to placental affection, ZIKV infection may lead to intrauterine growth retardation, miscarriage and fetal death. Polyhydramnios is also often seen (1). Although microencephaly is the most known clinical presentation, the characteristics of CZS can be the tip of the iceberg of other adverse or unknown outcomes (37). Infants might be born normal appearing manifesting delayed development and disabilities later in life.

5.1.5 ZIKV control – diagnostics and treatment

When ZIKV infection is suspected after travelling to endemic countries, women can be tested with PCR serology and presence of antibodies (IgM/IgG). If fetal infection is suspected, PCR can be performed on amnionic fluid, urine, blood, placenta, or other tissues, yet negative PCR test from amniotic fluid or umbilical cord cannot exclude ZIKV infection. Treatment of maternal infection is symptomatic and involves supportive care. There is today no cure or prevention of fetal infection (1). There are challenges with laboratory diagnostics as there is cross-reactivity in the antibody testing, therefore prenatal diagnosis of ZIKV infection is challenging (37).

No vaccine against ZIKV-mediated disease is currently available (1). Several vaccine candidates for ZIKV have been considered and the similarities to the other flavivirus is helpful in the vaccine development. Studies on these flaviviruses suggest that a vaccine with ENV binding antibodies can cause protection against ZIKV (38). The trials so far have involved animals (mice and monkeys), with some promising results providing short term protection. Mice pregnancy models did however detect ZIKV RNA in fetal tissues after the

vaccine, which does not seem promising for this vaccine's protective effect on the fetus. A recent phase 1 clinical study from the United States with 100 participants, published in February 2021, shows that over 80% of people with two vaccine doses had antibodies against ZIKV within a year, and no severe side effect was reported (39). This was a limited study on a small group in a nonendemic area, and whereas this approach is relevant for pregnant women and their fetus is unknown.

As the ZIKV cofactor TIM1 facilitates viral entry to placental cells and thereby entry to fetal circulation, a TIM1 inhibitor is also suggested as a possible target for ZIKV control (34).

As no vaccine is available to prevent ZIKV infection, other control strategies like mosquito protection must be applied (14). In Norway, Norwegian Institute of Public Health (FHI: Folkehelseinstituttet) has developed advice for pregnant women on travel abroad, as there is no risk of being affected in the Nordic countries. Unnecessary travels to endemic areas are recommended to be delayed if pregnant or planning on getting pregnant. If travelling to endemic areas, mosquito protection as well as protection during sexual activities is recommended (40). A recent ZIKV infection presumably provide long-term immunity and thereby protection against new infections in future pregnancies (1, 41).

5.2 COVID-19 during pregnancy

5.2.1 Clinical manifestations

The incubation time for SARS-CoV-2 is 0-14 days with an average of 5 days (16). The COVID-19 infection is likely to be asymptomatic in around 80% of cases, though different studies reports both higher and lower estimates (17).

The predominant clinical symptoms in pregnant women are reported similar to nonpregnant, including fever, cough, dyspnea and lymphocytopenia (19). A study published in September 2020 presents how pregnant and recent pregnant women show a set of symptoms that differs from other women with less fever, dyspnoea and myalgia (42). A more recent study from Turkey with 29 confirmed and 71 suspected SARS-CoV-2 infected pregnant women reports cough and myalgia as the leading symptoms (17). Norwegian Guidelines reports the predominant symptoms for infection in pregnant women as cough (41%) and fever (40%) (16). To date most pregnant women with COVID-19 are still asymptomatic or experience

mild symptoms, but SARS-CoV-2 during pregnancy can also lead to severe adverse outcome for other and offspring, including critical maternal disease signs with the need of mechanical ventilation (43). There are good arguments for a lower threshold for admitting pregnant women with confirmed or suspected SARS-CoV-2 infection to hospitals (16).

As the SARS-CoV-2 pandemic spread, isolation with distance to others was recommended to avoid transmission whilst developing a vaccine. The first vaccines were authorized in Europe starting December 2020, and as increasing parts of the population has been vaccinated, less cases of severe illness and deaths has been observed (44). The COVID-19 vaccines are highly effective and considered safe in a general population (44). Vaccination have significantly reduced the symptoms of COVID-19 and protects against severe disease in the general population (45).

Clinical manifestations have also shown to change during the pandemic as adaptive mutations occur. In December 2021, WHO reported on five variants of SARS-CoV-2 to be of concern (VOCs); Alpha, Beta, Gamma, Delta and Omicron. New mutations are reported to be more transmissible. The Alpha variant is thought to increase risk of hospitalization and mortality in adults (46). Alpha is also associated with increased need of respirational support for pregnant (16).Today, as of January 2022, Omicron is the dominant variant. Omicron has over 30 changes in the spike protein and is 2.8 times more infectious than Delta (46). Clinicians in South Africa were the first to report on the Omicron infections, and concluded that it affects also younger people, but with less severe symptoms than past variants (47).

5.2.2 Transmission of virus

The SARS-CoV-2 transmission route is primarily by respiratory droplets, airborne and by direct contact, similarly to the other coronaviruses (18). The virus enters the host cells by ACE2, which functions as a receptor and is predominantly located in in the alveolar cells of the lung (19). ACE2 is present in other tissues as well and are believed to be needed for the virus to infect.

From early on in the COVID-19 pandemic there was no evidence of the SARS-CoV-2 to cause vertical transmission. Transmission would require that there are target cells or receptors on the placenta to permit vertical transmission. Diriba et al. (2020) concluded from 39 studies, involving 1316 pregnant women, that none reported maternal-fetal transmission and suggest

this may be due to the low expression of ACE2 in maternal-fetal interface cells (48). The placenta is thereby thought to lack the machinery for transmission. Pique-Regi et al. (2020) suggest the same, and that the coronavirus utilizes the ACE2 receptor *and* the serine protease TMPRSS2 for cell entry. Additionally previous studies (Pique-Regi, 2019) found that the expression of ACE2 and TMPRSS2 in chorioamniotic membranes is low and that the co-transcription is insignificant (49). The same findings are confirmed by other scientists in 2021(50). Summarized, the current knowledge suggests that the SARS-CoV-2 is not able to infect the placenta directly and thereby not the fetus when in utero with intact membranes.

However, in vitro findings published in November 2021 showed how trophoblast cells of the placenta express high levels of other genes that may facilitate COVID-19 infection of the placenta. (51). The authors demonstrated *in vitro* that cell-entry proteins like DPP4 and CTSL can possibly assist and mediate SARS-CoV-2 infection, and replication in placental cells. The study suggests that the SARS-CoV-2 virus can use multiple routes and thereby mediate placental infection and replication of virus. Additionally, the expressions of TMRPSS2 is higher in the third trimester, which possibly can increase the risk of pregnancy complications and vertical transmission in late pregnancy (52). More research is needed to refine placental infection routes for SARS-CoV-2.

Vertical SARS-CoV-2 transmission during to delivery is not a general topic of concern (53). Norwegian guidelines recommend vaginal delivery in COVID-19 infected mothers (16), unless there are other obstetric complications that require caesarean delivery.

SARS-CoV-2 has been detected in breastmilk in some infected women, but is not thought to be a way of transmission to the newborn, as the virus does not seem to replicate within milk. In addition, there are protective mechanisms in the gastrointestinal tract of the infant. A transmitted mother will produce antibodies that will be transferred to the baby via breast milk (1).

5.2.3 Placental affection

A review regarding placental histopathological following SARS-CoV-2 infection published in August 2020 reports on a variety of abnormalities. The findings include maternal vascular malperfusion in 46% of the cases and fetal vascular malperfusion (FVM) in 35% from a total of 150 third trimester placentas (54). Placentas with FMV are associated with an increased

rate of stillbirth and intrauterine growth restriction (55). The same review highlights that a minority of infants and placentas tested positive and that the association between maternal COVID-19 infection and placental pathology is uncertain (54).

In addition to malperfusion other histopathological changes were observed (54). Placental inflammation signs were observed in 10 of 20 studies, indicating that COVID-19 disease can *affect* the placenta. The inflammatory changes in the placenta are however likely due to both maternal and fetal inflammatory response, and there is so far no evidence of SARS-CoV-2 directly infecting the placenta (56).

150 third trimester placentas	FVM	MVM	Inflammation in placenta
	35%	46%	Vilitis 9%
			Intervillositis 5%
			Chorioamnionitis 6%

Table 2: Placental findings with SARS-CoV-2 (54). MVM =maternal vascular malperfusion, FVM = fetal vascular malperfusion.

A more recent meta-analysis from a total of 56 studies concludes with a significant proportion of histopathological findings in placentas from women with SARS-CoV-2, especially hypoperfusion and inflammation (57). The 2020 data from Norway has also reported viral affection of placenta from a case of stillbirth, reflecting the findings from international studies where placental inflammation can occur in a minor of cases (58). As for placental malperfusion findings, there are no reports from Norway to be found yet.

Another meta-analysis showed that the risk of developing preeclampsia was higher due to SARS-CoV-2 infection, as was the risk of other clinical presentations of the preeclampsia syndrome; eclampsia and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. These risks were increased in one study both when the maternal infection was asymptomatic or symptomatic, and an association between SARS-CoV-2 and preeclampsia during pregnancy is suggested (59). Recent reports suggests that severe maternal outcome of COVID-19 is associated with increased development of gestational diabetes, preeclampsia (59), intrauterine fetal death and low birth weight. Especially serious illness in third trimester is associated with preterm birth (16).

As pregnancy is a state of increased inflammation, when compared to non-pregnancy, and preeclampsia a state of excessive generalized inflammation, when compared to normal pregnancy (60), the association of COVID-19 and increased risk of any forms of the heterogeneous preeclampsia syndrome is not surprising. The same goes for fetal growth restriction and preterm delivery, both associated with placental dysfunction, similarly to preeclampsia. The association between SARS-COV-2 and hypertensive disorders of pregnancy and other forms of placental dysfunction may rely on the population's general risk factors for preeclampsia, including rates of primiparity, chronic hypertension and obesity (60).

5.2.4 Outcomes for the pregnant and her offspring

Pregnancy was in the beginning not thought to intensify the symptoms of COVID-19 (16, 56), but as the pandemic spread amongst pregnant there were findings that SARS-CoV-2 affecting the maternal health, and pregnant women were seen to have an increased risk of being admitted to intensive care units (ICU). Although pregnant women represent a young population and therefore expected to present with mild symptoms, the need of mechanical ventilation has been more higher than non-pregnant of same age group (61).

United Kingdom first reported that 40 of 427 COVID-19 sick pregnant women (9%) during the period of March-April 2020 needed respiration support. Five of these women died. This gave a SARS-CoV-2 associated maternal mortality of 5,6 per 100 000 births. There were more miscarriages, stillbirths, and deaths among infants than in the control group, however the findings were not significant due to small numbers (62, 63). Another study reports that the risk of hospitalization is 3.5 times higher among pregnant infected women as compared to same non-pregnant control patients, again supporting pregnancy as a risk factor for the severity of COVID-19 disease (18).

The first six months (2020) of the pandemic generally reported increased risk of hospitalization, mechanical ventilation, ICU admission and preterm births (43), but no increased mortality risk for pregnant women. In contrast, a recent publication from Washington state, USA, reports on a higher mortality rate among pregnant women, as well as preterm birth (64).

Neonates born from infected women test mostly negative, and if COVID-19 is confirmed in the offspring, the symptoms are mild. An increase in admission of newborns have been observed where the mother is infected, compared to non-infected, but COVID-19 alone is not thought to cause severe illness for the infant (16). The timing of transmission in the few cases is unclear due to lack of knowledge regarding vertical transmission routes (43).

The immune response to presence of SARS-CoV-2 during pregnancy, both maternal and fetal, is important to investigate. Maternal IgG antibodies can be transferred across the placenta, and studies show that SARS-CoV-2 IgM and IgG is detected in neonates (43). However, this is not an evidence of transmission or infection in the fetus. Serology data from maternal and umbilical cord blood shows increased levels of IgG when the women is infected with SARS-CoV-2, and the levels depend on the severity of disease (43). Besides antibodies, other pro-inflammatory cytokines are observed in both the maternal and neonatal circulation. A cytokine storm in the circulation can lead to septic shock or multi-organ damage and patients with severe disease have higher levels of inflammatory secreting cells (65). The presence of increased cytokine levels such as IL-8 in neonates of infected mothers confirm that a cytokine response can occur. This indicates that besides a possible maternal cytokine storm, SARS-CoV-2 can lead to neonatal inflammation. However, SARS-CoV-2 RNA and proteins are not present in the placentas investigated (43).

The situation in Norway

The Medical Birth Registry of Norway (MBRN) did an extended gathering of data on pregnant women with COVID-19 who were admitted to hospital in Norway during 2020. Data from 2021 is not yet publicly available (January 2021). Table 3 presents data from MBRN on pregnant women with COVID-19 in Norway in the period of March – September 2020. There were a total of 89.585 deliveries during this period (58, 66). Among these, 213 women had confirmed COVID-19 test had been tested due to mild symptoms or due to close contact to other positive persons. Most of them were also in contact with the hospital due to other medical issues than COVID-19, or were attending the hospital due to delivery. Pregnant women in Norway has had the same risk of positive COVID-19 test as non-pregnant, but has had more often contact with the specialist health services (16), which is not surprising.

Pregnant with COVID-19	Admitted to hospital	Need of COVID-19 treatment	Need of ICU care
N=213	N=181 (85%)	N=32 (15%)	No number reported

Table 3: 2020 data from Medical Birth Registry of Norway (MBRN) (58, 66). ICU = intensive care unit.

Pregnant women admitted to hospital in Norway in 2020 due to COVID-19 were as few as 0,4 per 1000 delivery. Severe COVID-19 disease in third trimester is associated with an increased risk of preterm birth, especially between week 32 and 36 with delivery due to maternal disease or fetal distress (42, 63, 67). A few preterm deliveries (before week 37) have been reported in Norway during this period among the women in need of respiratory assistance, and these women were not vaccinated (58). The Norwegian numbers from 2020 is too small to permit analyses of the risk factors in general, but recent media reports of 2021 and 2022 suggest that vaccination status is essential for preventing adverse pregnancy outcomes, also in Norway (68).

Possible fetal complications reported due to COVID-19 include fetal growth restriction and preterm birth (18), but no increased risk of malformations has been reported so far (16). MBRN reported a few cases of miscarriage in women with COVID-19 from 2020 whereas other factors than COVID-19 were likely the cause for miscarriage (58). There are no public reports available on infants admitted to Neonatal Intensive Care Unit (NICU) in Norway from 2020 (16)

The Nordic Obstetric Surveillance Studies (NOSS) of COVID-19 found a 13.7% risk of neonatal intensive care unit admission in neonates of COVID-19 mothers. No stillbirths or neonatal deaths were reported in pregnancies with COVID-19 sick mothers.

5.2.5 SARS-CoV-2 control – diagnostics and treatment

When infection with SARS-CoV-2 is suspected, there should be a low threshold for PCR testing, especially for pregnant women, providing availability of testing capacity. Serology testing is not used as early diagnostics. Selftesting with a rapid screening test of the nasal cavity is commonly being used in 2022. Radiology like x-ray imaging and CT can be used when suspecting lung affection, which is permissible also in pregnant women due to a relatively low radiation exposure (1).

Norwegian guidelines suggest quarantine and postponement of any obstetric examination if possible in pregnant women with COVID-19. If moderate or severe COVID-19 disease, pregnant women should be admitted to hospital in a Medical Department and monitored as advised. The fetus should be monitored by Doppler once a day from week 24-28 and by CTG from week 28. Fetal lung maturation, induction and delivery is evaluated through interdisciplinary collaboration. Pregnant patients with mild symptoms admitted to hospital due to an obstetric indication should be monitored like any other patients. There are specific guidelines for delivery (1). There is no evidence for a benefit of separating the mother and infant after delivery, unless the mother needs intensive treatment or monitoring and is not capable of handling the newborn. Breastfeeding is recommended, but precautions like handwash, and in some cases face mask, are recommended to minimize risk of transmission between mother and infant (1).

There are ongoing trials regarding antiviral treatment and special concerns need to be taken as some antivirals are teratogenous. Norway is in general reluctant with experimental treatment, which makes sense as the disease burden in pregnant women hitherto has been low. Supportive care as well as potential intubation, immune modulation, thrombosis prophylaxis and possible complications are the strategies (1). Antivirals like Lopinavir and Ritonavir are seen as safe during pregnancy (53), but they are not available in Norway today (16).

As for vaccination against COVID-19 disease, the recommendations in the beginning of the pandemics did exclude pregnant women, due to lack of safety data. In Norway, The Guidelines from The Norwegian Association of Obstetrics and Gynecology (NGF: Norsk gynekologisk forening) stated in May 2021 (revised version 5) that the mRNA vaccines were likely safe in pregnancy and that vaccination should rely on a risk/benefit evaluation (69). FHI updated their public guidelines in August 2021 to recommend vaccination prior to and during pregnancy (70). FHI concludes that the vaccine protects both mother and infant from severe disease and adverse outcomes (58). In the 6th revised version of the NGF COVID-19 guideline, in November 2021, all pregnant women are recommended to be vaccinated as the general population (16), and that the two available mRNA vaccines in Norway (BioNTech/Pfizer (Comirnaty) and Moderna (Spikevax)) are considered equal in effect and safety for pregnant women. The Royal College of Obstetricians Guidelines stated on 7th of May that vaccination of pregnant women could follow the normal vaccination guidelines for non-pregnant persons (71). In November 2021, the European Board and College of Obstetrics

and Gynecology (EBCOG) also concluded that the evidence is sufficient to show that vaccine against Covid-19 during pregnancy is safe. All pregnant woman are urged to get vaccinated as well as having a booster dose (72).

MBRN data from 2021 reports that none of the pregnant women treated for Covid-19 in Norway were fully vaccinated, but the numbers are small (58). Second and third trimester vaccination is potential causing passive immunity in the child after delivery, as antibodies might pass the placenta (61). Vaccination during pregnancy varies with regions across the world (61). The 2022 vaccination status in Norway is relatively good compared to many other countries and FHI estimate that 7 of 10 pregnant women are vaccinated (73).

There is evidence of protection to new infection after having undergone COVID-19 infection, however the duration of how long such protection lasts is uncertain (16).

5.3 Breastfeeding

Viral particles have been detected in breast milk of mothers infected with either ZIKV or SARS-CoV-2, however breastfeeding is likely not a significant route of transmission to the offspring. Breastfeeding is strongly recommended in general internationally (16). WHO and FHI both recommended breastfeeding in infected mothers where the benefits surpass the slight and unknown possibility of a viral transmission to the offspring. None of the two viruses are thought to have a severe impact on the infant if entering with breastmilk. As for SARS-CoV-2 the virus is not confirmed to replicate within breastmilk (16). In addition, the gastrointestinal system of the infant is thought to break down viral particles. WHO recommendations regarding ZIKV conclude that breastfeeding should be done according to normal infant feeding guidelines (74), whereas mothers with suspected or confirmed Covid-19 are advised to take precautions with hand hygiene.

5.4 Differences and similarities of ZIKV and SARS-CoV-2 infections in pregnancy

The outcome of viral infections like ZIKV and SARS-CoV-19 during pregnancy can be adverse and vary in severity of outcome for both mother and fetus. The complexity of pregnancy physiology as well as the involvement of two individual makes the picture more compound.

The increase of hCG, progesterone and estrogen are besides promoting tolerance towards the developing fetus, assumed to make the upper respiratory tract more susceptible to respiratory infections as the mucous is thickened with edema (75). There is clinical evidence that pregnancy induces systemically immunologic change with altered cellular immunity and an enhanced humoral immune system (76). Due to the immunological changes during pregnancy, the pregnant woman is recommended to take special precautions regarding both infections.

There is evidence that prenatal exposure to ZIKV is associated with a significant risk, up to 20%, of innate neurological abnormalities or CZS for the fetus. When it comes to SARS-CoV-2, the outcome still seems more uncertain and less severe, but as the data is based on a short time of period and the conclusions from small population numbers may be uncertain. These two epidemics have significant parallels in terms of the prognostic uncertainties, the limited diagnostics and therapeutics (18). In contrast, vaccination is now available for SARS-COV-2, and seems to reduce the risk of severe illness among pregnant with COVID-19 significantly. Therefore, urging also pregnant women to vaccinate is the most important ongoing mission to reduce the adverse effects of a COVID-19 infection in pregnancy. As for ZIKA, where no vaccine is available, the sensible recommendations is to avoid travelling to endemic areas, and to use mosquito net protection if one must stay in such an area.

The main concern regarding ZIKV is the possible detrimental outcome for the infant. COVID-19, on the other hand, exerts is effect depending on maternal health and vaccination status, impacting the pregnancy outcome for mother and child (18).

Considering timing of infection, the first trimester is likely the highest risk for developing the Congenital Zika Syndrome (12), as it represents the more vulnerable time for fetal developmental disorders. As for COVID-19, the third trimester is thought to be the more critical period of infection for the mother, and so far there has not been reported increased risk of stillbirth or congenital abnormalities with infection at early infection onset in pregnancy (16).

Regarding transmission route, the findings on the specific receptors for both ZIKV and cytomegalovirus (CMV) are in strong contrast to the knowledge we have so far regarding SARS-CoV-2. ZIKV can enter HBCs in placental tissues followed by fetal circulation and

bind to AXL receptors in the developing fetus. Congenital infection is thereby likely to occur. The findings regarding COVID-19 so far hold that transplacental transmission of SARS-Cov-2 is unlikely due to the absent expression of ACE2 and possibly TMPRSS2. However, as the virus has been detected in some placentas, the question remains open for debate and more studies are warranted. Other transport mechanisms are thought to be possible for SARS-CoV-2, such as DPP4 and CTSL assisted cell-entry. Whatever the small chances are for direct SARS-CoV-2 uptake in the placental cells, recent reports suggest that excessive maternal inflammation status in a sick pregnant woman with COVID-19 infection, is paralleled by similar excessive inflammatory changes in cord blood (43). This again supports the active vaccination campaigns in order to reduce the numbers of and severity of disease in pregnant women, in order to reduce also the likelihood of severe adverse outcomes for mother and child (68).

Table 4 highlights some central aspects from infection with ZIKV and SARS-CoV-2 during pregnancy.

	ZIKV	**SARS-CoV-19**
Vector and transmission	Flavivirus in mosquitoes Sexual, blood-borne	Coronavirus in droplets Airborne
Vertical transmission	Occurs. Congenital infection is likely through specific receptors	Not confirmed
Maternal symptoms	Asymptomatic or mild flu-like	Varies from asymptomatic or mild flu-like to severe and in need of intensive care
Placental affection	Nonspecific inflammation signs	Maternal and fetal vascular malperfusion Placental inflammation signs
Possible fetal outcome	Stillbirth Preterm birth CZS (Congeital Zica Syndrome) Growth deficit Developmental delay	Often normal Growth restriction Stillbirth Preterm birth
Breastfeeding	Virus findings in breast milk Breastfeeding recommended	Possible virus findings in breast milk Breastfeeding recommended
Vaccine and treatment	No vaccine available Preventive treatment Supportive care	Vaccine recommended Experimental antivirals Supportive care

Table 4: Summary of the findings of ZIKV and SARS-CoV-2 infections during pregnancy

VI Discussion

This project thesis aimed to investigate the outcome of maternal and neonatal ZIKV and SARS-SoV-2 infection during pregnancy. The thesis has summarized that there are several adverse outcomes and concerns regarding these infections, and as new knowledge is presented the long-term effects will be less uncertain.

As pregnant women are at a greater risk of complications and severe disease from some viruses, they were identified as a vulnerable group as the COVID-19 pandemic unfolded (77). There were in the beginning of 2020 great insecurities about the situation and following health outcomes. The wealthier parts of the world were then able to take additional actions. In Norway the numbers of COVID-19 pregnant women were few at the beginning of the pandemic likely due to great adherence to the recommended social isolation. This contrasts widely to what we saw in the epidemic of ZIKV in 2015/16, where the link between virus and outcome were seen in retrospective.

The maps on page 7 show how ZIKV and SARS-CoV-2 have transmitted globally, and whereas ZIKV seems to be limited to the tropical belt, the COVID-19 infection is spreading worldwide. Pregnant women thereby have a geographical defined exposure to ZIKV, and special concerns can be taken to the reduce the risk of severe fetal outcomes, by protecting from mosquito bites and avoiding sexual activities with potentially infected partners. However, living in areas with this mosquito borne virus induces a greater risk of transmission and thereby adverse fetal outcome.

Besides the geographical differences, data from both Norway and other countries demonstrate how social and economic differences affects the outcome of viral infections like Zika and COVID-19 in pregnancy. Social and economic inequalities increase the risk of health burden in both epidemics, as seen from more defenceless communities (18). The outcome for COVID-19 affected pregnant women seem to depend on the maternal health and the vaccination rate.

The present knowledge is that the maternal risk factors, including vaccination status, is crucial for the severity of COVID-19 disease in pregnancy both for the mother and fetus. The Zika virus has a very different health effect, as maternal risk factors are not identified other than

the geographical ones, and where asymptomatic maternal infection can cause serious adverse outcome for the infant independently of maternal symptoms and signs. The more challenging topics regarding ZIKV includes the vaccine development, diagnostic methods, clinical management, and potential treatment. Screenings of suspected foetal brain abnormalities in ZIKV only have a detection rate of 83% in infected pregnant women (14). Also, a detection of severe fetal malformations after ZIKV infection would usually take place long after the gestational age limit for legal termination of pregnancy in most countries.

An article published in The Journal of the Norwegian Medical Association (Tidsskrift for Den norske legeforening) from 2016 discusses the consequences of the Zika epidemic and how poor pregnant women are affected more severely than rich (78). Whereas health authorities of South America advised women to postpone their pregnancies during the ZIKV endemic, the responsibility of not delivering more disabled babies relied upon the women herself, which seems very unfair. Potential fathers are left without responsibility, despite transmission also occurring sexually, and the many young expecting mothers are secondarily thought to be at higher risk of unsafe abortions due to fear and lack of information and maternal health support. Abortions are illegal in many countries and terminating pregnancy unsafe can lead to dangerous complications (78). The same article also discusses how poor pregnant women in specific areas of the world are at greater risk of Zika transmission and infection due to their way of life. This demonstrates the socioeconomical differences we can see in all aspects of healthcare and thereby also in the epidemics of ZIKV and SARS-CoV-2. The complication rate of infections heavily relies on socio-economic status. Protective mechanisms for ZIKV includes covering clothes, sanitizing water ponds and mosquito protection (78), which can be rather challenging if living in poor conditions.

To actualize this with the ongoing pandemic of COVID-19 and the challenges in Norway, economic inequalities amplify the risk burden of both diseases (18). How are the government and health authorities taking responsibility for minimizing these inequalities and possible imbalanced outcome today?

Hospital services in Norway are meant to be equally available for all. In the ongoing pandemic, both social support and evidence-based information is very important to provide, and it is challenging to reach all citizens and secure trust between health care advisors and users across all socioeconomic and cultural background. In the beginning of the COVID-19

pandemic in early 2020 there was little knowledge on the effects of infection during pregnancy, and pregnant women were like others isolated in their homes whereas data on adverse pregnancy outcomes were few. In contrast, during the winter of 2021/2022 Norwegian hospital doctors informed the press about cases of severely ill pregnant women in ICUs, where none were vaccinated. The advice is as of January 2022 clear and consistent throughout Europe and the remaining world; pregnant women are urged to take the vaccine (a mRNA variant, not a virus vector-based vaccine), and the vaccine protects against severe outcomes in mother and offspring (72).

This vaccination advice has however not been consent from the beginning of the SARS-CoV-2 pandemics, as the updated recommendations for pregnant women to be vaccinated in Norway was published August and November 2021 (70). Risk of serious illness among pregnant women with COVID-19 is still described as low, however international studies suggest an increased risk following advancing trimesters. Therefore, vaccines were in August 2021 recommended for all in 2nd and 3rd trimester, as well in the first trimester for pregnant women at increased risk of adverse COVID-19 outcomes, such as women with coronary diseases. The EBCOG Press Release from November declared that COVID-19 infection carries a greater risk than the vaccine and urges *all* pregnant women to be vaccinated, paralleled by the Norwegian guidelines in November 2021 (72), recommending vaccination in all three trimesters, when the woman was being offered the vaccine. This indicates how knowledge on new disease becomes available along the way. A change in recommendations with new updates can negatively affect different socioeconomic groups, possibly especially affecting newly immigrated populations with limited reading or listening to news in Norwegian and less contacts with the Norwegian population. Misinformation by social media is also influencing our risk perception and plays a complex role, possibly affecting ore of the less educated population than the educated one.

The ethics in publication of studies is also a relevant topic to discuss. Studies involving a small number of people published too early before adverse effects are likely to appear (as they are often rare) can mislead and play a role in pregnant women's risk perception as well as the health care provided. On the other hand, there are challenges regarding clinical trials for pregnant women due to the importance of an individualized approach in the management of pregnant women. Many studies, however, do not differ between hospitalizations due to

COVID-19 and other reasons like obstetric treatment (16), making the rate of clinically relevant infections hard to understand for the public.

In addition to the maternal immune system changes and that viruses possible affect the placenta, the physiological changes that occur during pregnancy is thought to play an important role in any infectious disease. This has not been a topic for this thesis. The maternal torso and lung volumes undergoes anatomical changes and the respirational frequency increases during pregnancy. This can be thought to make the pregnant woman more vulnerable to respirational viruses like SARS-CoV-2.

Another important theory to be investigated is how the cytokine storm or cytokine release (CRS) that can occur during COVID-19 triggers an inflammation response in the fetus, despite absence of the viral microorganism within the fetal circulation (43). If this occurs, the excessive fetal circulating cytokine levels can be thought to possibly trigger CNS affection in the developing fetus and thereby possibly share some similarities to ZIKV affection. This needs further investigation and long-term follow-up of the children from severely affected COVID-19 mothers.

Cohort studies of other infections associate maternal fever during pregnancy with development of attention deficit disorders (ADD) in children. As pyrexia is the main symptom of COVID-19 disease, this possible association to ADD is also suggested in COVID-19 (19), since its long-term outcomes for both mother and infant are unknown. Emerging studies point to Long Covid following COVID-19 infections, including fatigue symptoms. Some studies point to differences between women and men, in that women seem to experience less short-time adverse effects than men, but more long-term health problems after COVID-19 (79). Whether Long Covid will be a challenge also in women following pregnancies affected by COVID-19, remains to be seen.

In the beginning of the COVID-19 pandemic there was a report of decreased preterm birth on Denmark (80). However, later population-based data from Norway, Sweden and Denmark show that there is no consistent evidence in altered preterm delivery rates due to the pandemic so far (81).

VII Conclusions

This project thesis has addressed central topics regarding Zika and COVID-19 infection during pregnancy, some aspects of adverse health outcomes and current knowledge regarding disease prevention and management. Many dimensions both for individuals and communities nationally and globally need further investigation.

Pregnant women do not seem to be more likely infected by either ZIKV or SARS-CoV-2 (82). Regarding Zika infection, the mother is likely to be asymptomatic or with mild symptoms. This in contrast to COVID-19 where pregnant women are at increased risk of hospitalisation (82). Pre-existing chronic conditions seem to be of great importance in mediating the severity of disease presentation.

When epidemics occur, the interaction to each specific antigen must be investigated to find the effects on the placenta and fetus, and optimized preventive and therapeutic strategies must be developed. The physiological and immunological changes of pregnancy make guidelines and healthcare more complex than for non-pregnant adults.

The epidemic of Zika and the COVID-19 pandemic have similarities, including community transmission and prognostic uncertainty as well as sharing a perinatal risk. In contrast, the vectors, transmission routes and epidemiology differ. Both infections have limited therapeutics, but a vaccine was rapidly developed against SARS-CoV-2 infections which not only reduced the infection rates, but also the severity of COVID-19 disease, if infected.

Further research is needed to identify the maternal and fetal total effects and outcomes of COVID-19 in pregnancy. We have a relatively clear image of Zika after the 2015-2016 epidemic, but both improved diagnostic and therapeutic research is needed and a vaccine is strongly desired. Women of reproductive age and their infants are especially vulnerable to the outcome of Zika infection, whereas pregnant women with COVID-19 have the possibility of protection from severe adverse outcomes with vaccination. However, the long-term effects of COVID-19 on mother and child are still uncertain. We are still in the ongoing pandemic and how it will affect future generations worldwide remain unknown. As new virus mutations occur, the disease panorama in pregnant women is also likely to be changing.

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