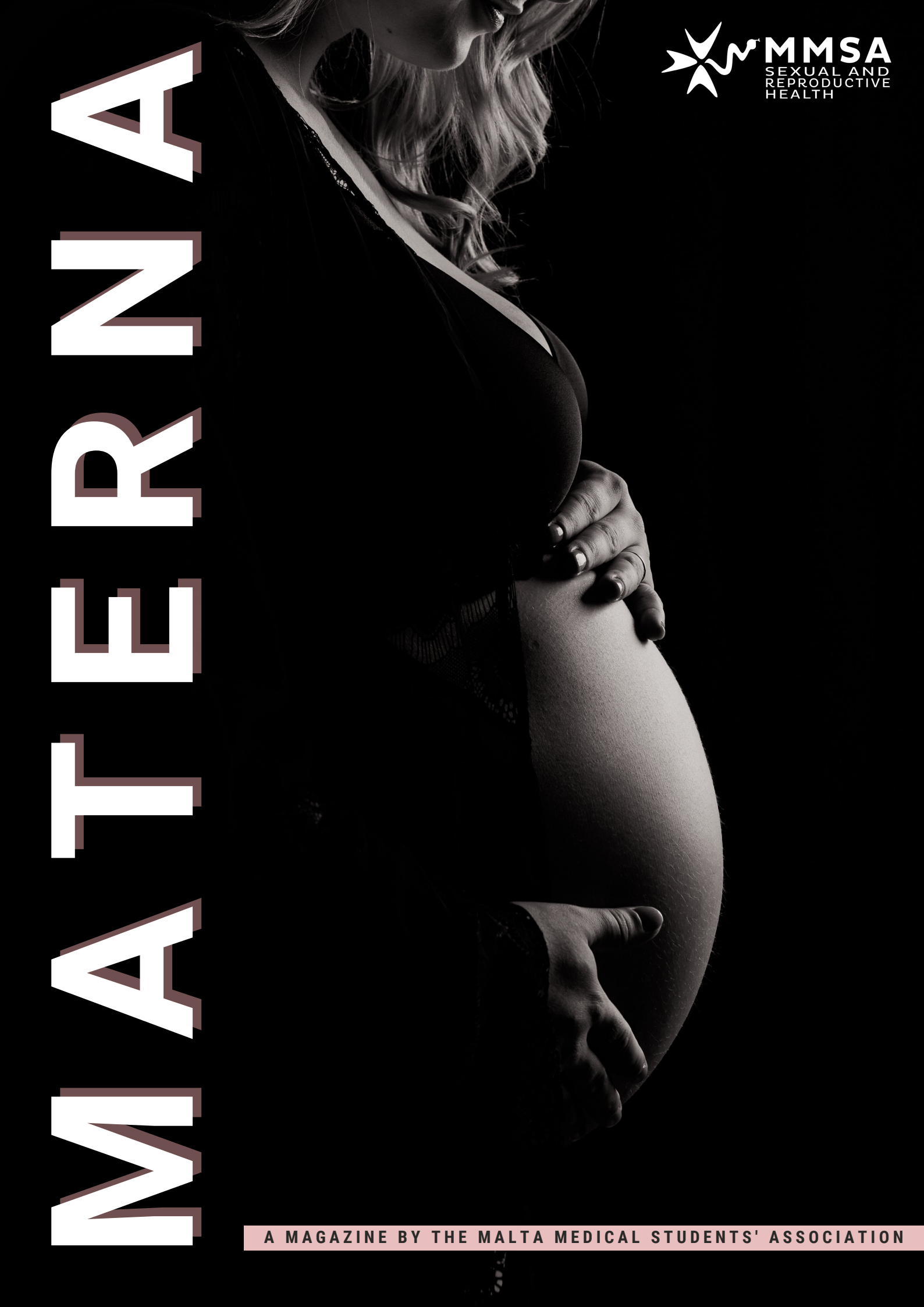
MATERNA



MMSA
SEXUAL AND REPRODUCTIVE HEALTH

A MAGAZINE BY THE MALTA MEDICAL STUDENTS' ASSOCIATION

TABLE OF *contents*

“A mother is she who can take the place of all others but whose place no one else can take”

CARDINAL MERMILLOD

Foreword Message

PROF JEAN CALLEJA-AGIUS

In Europe, about 5 million live births occur each year. While this is generally considered as a positive life experience for mothers and their families, it is estimated that 18% of women will develop depression during pregnancy, 13-20% of women will develop postnatal depression within the first 12 weeks of childbirth, and for 8% of women, this extends beyond the first year. This negatively impacts both the mother and the offspring, as well as the rest of the family.

As described in the article by Ms Gabrielle Grixti, psychiatric conditions such as post-natal depression are prevalent among all societies, irrespective of age, background and education. Of course, women with low socio-economic status are more at risk due to concurrent factors, such as poor nutrition, poor hygiene and malnutrition. Alcohol abuse, while prevalent among all strata of society, can exacerbate psychiatric conditions, and vice-versa, spiralling down into a vicious cycle. Worse still is the consequent foetal alcohol syndrome which may affect the offspring, as outlined in the article authored by Mr Robert Pisani.

Health inequalities are very much present in modern day society. The ongoing COVID-19 pandemic has highlighted this discrepancy in access to basic healthcare even more. Maternity care has of course suffered the brunt of the pandemic, limiting the access to care and antenatal follow up. This meant that conditions like congenital infections for example, may not be picked up early. Congenital infections, including cytomegalovirus, can severely affect the developing foetus, as highlighted in the review by Ms Maia Rapa.

Fertility awareness and infertility treatment are also very important in the management of women of reproductive years. Premature ovarian failure, which has been reviewed by Ms Emma Camilleri, is one of the possible causes of infertility in young women. This condition also has long lasting effects on the patient's health, due to the detrimental effects of early menopause.

In the case of medical students and future medical doctors, SCORA has an important role to play in raising awareness about the importance of professional fertility counselling, as well as maternity care, from pre-conception till birth, and beyond. Access to safe antenatal, intrapartum and postnatal care is a basic human right.

Childbirth is a major life event for mothers and their families, and it is one of those moments where a patient is most vulnerable. SCORA, which I am proud to have been the one to set it up way back in 1997 in my third year of the MD course, is very well-placed to empower medical students to be the voice of the vulnerable, and compassionate to those who seek medical help, even when in desperate situations when there is little offer.

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Foreword Message

OWEN CACHIA

As the officer on Sexual and Reproductive Health and Rights' within the Malta Medical Students' Association, it is with great honor to be introducing to you this year's edition of MATERNA. This journal is composed of different pieces written by medical students and MMSA members which were extensively reviewed by local academics. The numerous articles focus on different, yet equally important, aspects of maternal health, pregnancy and fertility. I encourage all of our readers to sit back, read through this journal and appreciate the work and passion of tomorrow's doctors.

Maternal Health refers to the health of women during pregnancy, childbirth and the postnatal period. The World Health Organization states that each stage should be a positive experience, ensuring women and their babies reach their full potential for health and well-being. Every pregnancy and birth is unique, therefore, it is extremely important to address inequalities that affect health outcomes in order to ensure that all women have access to respectful and high-quality maternity care.

I would like to thank all the authors for taking this up and submitting their magnificent work to our journal; this would not be possible without their contribution. Furthermore, I would like to express my gratitude to Prof. Jean Calleja Agius for her continuous support towards this journal during every step of the way. I would also like to thank my hardworking team, especially, Adrienne Gatt and Jennifer Xuereb, together with my assistant, Emma Azzopardi, for their utmost dedication from the beginning of the term. Finally, I would like to thank the Public Relations Team, especially Amy Carabott for bringing this journal to life with her wonderful design.

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A Brief Overview On Premature Ovarian Failure

EMMA CAMILLERI

INTRODUCTION

Menopause is a physiological process that occurs approximately at the age of 51 where a female will no longer undergo menses due to the scarcity of ovarian follicles(1,2). However, in premature ovarian failure (POF) also known as premature ovarian insufficiency (POI) and hypergonadotropic ovarian failure, there is a significant decrease in ovarian function and substantial reduction in ovarian follicles after puberty and before the age of 40(3,4). Moraes-Ruehsen and Jones had first described this disease as non-physiological amenorrhoea in non-menopausal women and in 1950. Atria had recounted the characteristics that POI patients would present with, secondary to hypergonadotropic hypoestrogenism(5). Although, occasional resumption of ovarian function can be seen in such patients and spontaneous pregnancies can occur, being diagnosed with POF can have a mental and physical toll on one's health(2,5).

DIAGNOSIS AND CLINICAL PICTURE

POF is a complex heterogeneous disease that affects 0.1% of females who are 30 years of age or younger, while 1% are diagnosed by the age of 40(2). In addition, a greater prevalence of patients with POI was noted in countries having an intermediate or low human development index(6).

The symptoms of POI can vary across a broad spectrum from one patient to another as this disease can either evolve over the years or spontaneously. POF can be broadly classified into two groups in relation to how it may present. Up to 10% of POF patients present with the most severe form of the disease, where there is a complete absence of pubertal development together with primary amenorrhea, whilst the majority of patients undergo normal pubertal development and eventually show signs of secondary amenorrhoea and menopausal symptoms later on in life(6,7). Such symptoms may include hot flushes, increased sweating, decreased libido, tachycardia, mood swings, reduced sleep quality, dyspareunia, mucous dryness and hair loss due to oestrogen deficiency. Interestingly, these symptoms are not usually seen in patients with primary amenorrhea since their body was never exposed to oestrogen. Furthermore, patients may also be diagnosed with POF when visiting a fertility clinic due to having difficulties with conceiving(3,6,7). Therefore, since the clinical picture that patients may present with is not clear cut and always indicative of POF, tests need to be carried out to eliminate other diseases like polycystic ovarian syndrome (PCOS), hypothalamic amenorrhoea caused by stress or anorexia and pathologies like pituitary tumours that influence the hypothalamic-pituitary-gonadal (HPG) axis(3).

Blood analysis in POF patients shows lower oestradiol (<20pg/ml), anti-mÜllerian hormone (AMH) (<1.5ng/ml) and inhibin B levels as well as increased follicle stimulating hormone (FSH) (>25IU/L) levels, when taken on two separate occasions with a one-month interval(7–9). Furthermore, obtaining AMH levels indicates the extent of ovarian reserve(5).

DIAGNOSING POF HISTOLOGICALLY

When taking a closer look at the histological appearance of the ovaries, the ovaries' morphology in POF can be classified in two ways:

- In Type 1, also known as the afollicular form, the ovaries are observed to have no ovarian follicles. This can be either due to the depletion of follicles during embryonic development or shortly after birth. As a result, the ovaries would appear smaller having fibrous stroma. Causes include ovarian dysgenesis, chromosomal mutations and sex development disorders(5,6).

- In Type 2, which is the follicular form, follicles are still identified in the ovary meaning that ovarian function is still present to a certain extent. This type can be described in 3 ways: a) oophoritis; b) scarce follicles; or c) abundant primordial follicles in ovaries which is usually associated with resistant ovary syndrome (ROS). Type 2 can lead to the Type 1 form of POI(5,6).

Having a clearer understanding of the ovarian morphology and histology in POF would help in understanding the aetiology, pathogenesis, severity of the disease and what treatments would be best for the patient(6).

CAUSES OF POF

POF is a highly oligogenic and multifactorial disease that can have various aetiologies as seen in Figure 1. However, sadly, up to 90% of cases are of unknown origin(7,10).

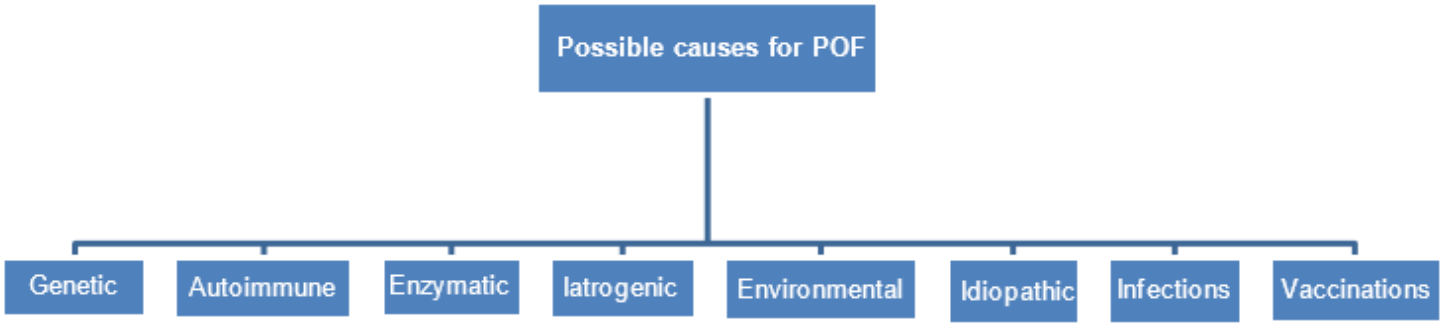

Figure 1: *Possible aetiologies for POF.3*

AUTOIMMUNE

POI may be caused by the presence of anti-ovarian antibodies which would lead to ovarian dysfunction. Interestingly, 20% of POF patients are usually diagnosed with other autoimmune diseases as seen in Table 1(7,10). Indeed, the most associated autoimmune disease with POF is Hashimoto's disease and autoimmune hypothyroidism followed by Addison's disease(2,5). Autoimmune regulator (AIRE) gene mutations can also lead to a phenomenon known as autoimmune polyglandular syndrome (APS), meaning that patients can develop other autoimmune disorders. Studies have shown that some patients having Addison's disease were diagnosed with POF 8-14 years prior. One must note that screening for anti-ovarian antibodies is not a reliable method to diagnose POF(5,7,11).

Autoimmune Diseases Associated with POI	
Rheumatoid arthritis	Systemic lupus erythematosus
Albinism	Coeliac disease
Addison's disease	Myasthenia gravis
Hashimoto's disease	Type 1 diabetes mellitus

Table 1: *Autoimmune diseases associated with POI (3,5)*

GENETIC

Up to 40% of POI cases account for genetic mutations due to its high genetic predilection, especially when concerning the X chromosome. In fact, more than 50 gene mutations can contribute to this disease. As seen in Table 2, various genetic mutations can influence the development and physiology of the ovaries, leading to POF(6,9,12).

Gene involved in mutation	**Effect**
Factor in germline alpha (FIGLA)	Loss of primordial follicles
Newborn ovary homeobox (NOBOX)	Loss of oocytes at birth
Forkhead box L2 (FOXL2), nuclear receptorsubfamily-five group A member 1 (NRSAA1), WT1	Impacts folliculogenesis
LHR	May cause primary or secondary amenorrhea
FSHR	May cause secondary amenorrhea

Table 2: *Genetic mutations associated with POF (3,6,7)*

Moreover, CGG repeats found in the fragile X mental retardation 1 (FMR1) gene in Fragile X syndrome are strongly linked with POF if the female inherits the permutation. However, if the normal or full mutation is passed down to the female, she is no longer at risk for POI. Additionally, downregulation of non-coding ribonucleic acids (nc-RNA) and Turner's syndrome have also been linked to POI(5,7). Genetic mutations leading to enzymatic deficiencies such as those concerning cholesterol desmolase, 17a-hydroxylase and aromatase can contribute to POF too(13,14).

ENVIRONMENTAL CAUSES & INFECTION

Malaria, tuberculosis, cytomegalovirus, mumps, varicella and other infectious diseases can also lead to POF(5). In addition, elevated levels of pro-inflammatory agents like cytokines and interleukin 6 have an undesirable influence on oocyte quality and abundance. Although these events have been described in ovarian inflammation, a direct link to the causation of POF has not been observed yet(15).

Smoking can also mediate the development of POI since the smoke has polycyclic aromatic hydrocarbons (PAHs) which upon binding to the aryl hydrocarbon receptor (AHR) on the oocyte, it will promote the activation of the Bax gene which is a pro-apoptotic gene. As a result, this stimulates the death of oocytes causing oocyte depletion and thus POI(13,16).

IATROGENIC

Radiotherapy, chemotherapy and surgical treatment (eg. oophorectomy) can cause permanent and irrevocable damage to the ovaries leading to POI(5). There have been case reports that the human papillomavirus vaccine (HPV4) can cause amenorrhea, oligomenorrhea, autoantibodies, depressed oestradiol levels and elevated FSH levels as well as premature menopause, thus creating a possible link between the vaccine and POF. Although, this may be due to the post-vaccination autoimmune phenomenon, not enough research and evidence has been presented to solidify the connection between the two(17,18).

POF AND ITS COMPLICATIONS

Since in POF, ovarian dysfunction is present, oestrogen is not being produced. Therefore this would lead to oestrogen deficiency and thus a decrease in bone marrow density. In addition, low free and total T levels seen in POI also contribute to a reduction in bone density. This increases the risk of such patients developing osteopenia, osteoporosis or easily fracturing a bone(5,7,19).

An increase in morbidity and mortality is also seen in patients with untreated and uncontrolled POF due to their risk of developing cardiovascular diseases such as atherosclerosis, hypercholesterolemia, strokes and ischaemic heart diseas(7).

Being diagnosed with POF can be devastating for many women, especially on an emotional level since their reproductive life span has been drastically decreased. These patients have been known to struggle with anxiety, stress, depression, relationship problems with fears of annulment, reduced self-esteem and a poor quality of life. Thus, apart from providing the patient with the necessary treatment, psychological support should be considered(7,20). However,although POI negatively impacts fertility, 10% of women with POI are able to conceive and carry to term since 25% of patients can ovulate spontaneously due to the ovaries' erratic function(7).

Undergoing a bilateral oophorectomy before the typical age of menopause would result in no ovarian function following the surgery, resulting in spontaneous surgical POI. This iatrogenic cause for POF has been linked to a reduced neurocognitive function, especially if the surgery is performed at a young age. This increases the patient's risk of developing Alzheimer's disease later on. However, evidence has shown that by administering hormone replacement therapy (HRT) as soon as possible following the surgery, decreases the decline in cognition and thus the risk for other neurological diseases(7,21).

Oestradiol is vital in maintaining outer hair cell function in the ear, and since oestradiol levels are reduced in POF, hearing is negatively impacted in these women. However, further studies on the impact of inner ear function in POF patients are required(22).

CORONAVIRUS DISEASE OF 2019 (COVID-19) AND POF

The respiratory, central nervous and cardiovascular systems are the main areas where COVID-19 infects and invades cells by binding to angiotensin-converting enzyme 2 (ACE 2) receptors(23).

Prolonged inflammation by COVID-19, termed as Long COVID, can also impact the reproductive system negatively due to the presence of ACE 2 in the ovaries which are vital for folliculogenesis, ovulation and luteal angiogenesis. Thus any alteration in ACE 2 activity and angiotensin II availability can easily lead to POF and infertility(23).

To date, there is one case report of a woman who has shown signs of infertility and oligomenorrhea after infection with COVID-19 the year previously(23). After ruling out any other possible causes for her symptoms, it was concluded that COVID-19 had led to POF by modulating ACE 2 expression in the ovaries(23).

TREATMENT AND MANAGEMENT OF POF

HRT, which is a combination of oestrogen and progesterone hormones, is recommended until the natural age of menopause (~50 years) in POF. This helps alleviate the effects and potential risks for certain diseases like atherosclerosis and osteoporosis due to oestrogen deficiency. Patients with a history of ovarian and breast cancer are advised against such treatment. In addition to oestrogen supplementation, adequate calcium intake, maintaining a healthy lifestyle and daily physical activity is advised(2,7,21).

Hormone Replacement Therapy

HRT, which is a combination of oestrogen and progesterone hormones, is recommended until the natural age of menopause (~50 years) in POF. This helps alleviate the effects and potential risks for

certain diseases like atherosclerosis and osteoporosis due to oestrogen deficiency. Patients with a history of ovarian and breast cancer are advised against such treatment. In addition to oestrogen supplementation, adequate calcium intake, maintaining a healthy lifestyle and daily physical activity is advised(2,7,21).

Immunomodulation Therapy

This treatment is only viable if the underlying cause of POF is an autoimmune response resulting in ovarian dysfunction. In this case, corticosteroids and monoclonal antibodies are used for immunosuppression(5,12).

Dehydroepiandrosterone (DHEA) Supplementation

In the ovaries, DHEA promotes follicular steroidogenesis and oestradiol synthesis. When patients suffering from POF are given DHEA, it prevents miscarriages, increases their chances of conceiving and improves in-vitro fertilization (IVF) outcomes(5). However, patients having normal adrenal function should not be given DHEA supplementation(5,12).

Melatonin Supplementation

FSH, luteinising hormone (LH), androgen and oestrogen receptors are found in the pineal gland which is responsible for melatonin synthesis(5). Melatonin has been described as a time-keeping hormone due to its ability to control pituitary hormone secretions. Although it is believed that melatonin, which is also found in follicular fluid, supports folliculogenesis, reinstates fertility and prevents depression following menopause, further studies are required to determine this hormone's exact role in ovarian function(5,12).

In-Vitro Activation (IVA)

If a female with POF wants to start a family, apart from oocyte donation and in-vitro fertilisation, IVA is another option that allows the female to have her own genetically and biological children since intracellular signalling pathways responsible for folliculogenesis are manipulated by pharmacological techniques to recharge and activate residual dormant primordial follicles(24). Although, oocyte maturity is enhanced in IVA, this treatment becomes less effective the older the patient's age due to reduced oocyte quality(25).

Stem Cell Therapy

Although stem cells taken from different parts of the body cannot improve oocyte quality, they do

enhance folliculogenesis, local ovarian vascularization, and follicle and stromal cell proliferation. Stem cells also have the ability to decrease cell apoptosis and follicular atresia. Healthy and successful pregnancies have been reported in POF patients upon undergoing bone marrow-derived stem cell therapy(26).

Furthermore, similar results have been reported using platelet-rich autologous plasma (PRP) therapy which promotes ovarian rejuvenation. PRP has been proven to increase FSH, LH, oestradiol and AMH levels. As a result, this improves the fertility of POI patients(27).

Additionally, small extracellular vesicles obtained from stem cells also have the potential to restore ovarian function to a certain extent. These vesicles can activate phosphatidylinositol-3-kinase and protein kinase B (PI3K-AKT), sirtuin (SIRT) and SIRT7 signalling pathways that play a vital role in folliculogenesis, granulosa cell proliferation and apoptosis regulation.

CONCLUSION

The tendency of people to have children at an older age is increasing. As a result, a woman's reproductive life span would be shorter by the time she would want to have children. Therefore, one can only imagine how devastating it would be to be diagnosed with POF. Thus, if one begins to experience symptoms pointing to POI, it is important to contact the healthcare provider and get tested for POF and to discuss the possible treatments and complications that may arise. Furthermore, follow-up visits and monitoring patients with POF in a holistic approach is recommended.

Finally, although several treatments are available, further studies are needed to increase our understanding of the disease's aetiology, how Long COVID complications resulting in POF can be prevented and how treatments concerning melatonin supplementation, ovarian stem cell therapy and rejuvenation can be improved, to decrease the emotional and physical stress of women with POF.

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Congenital Cytomegalovirus Infection

MAIA RAPA

Cytomegalovirus (CMV) is an enveloped double-stranded DNAvirus found commonly worldwide with a seroprevalence ranging from 45% to 100% (1,2). Congenital cytomegalovirus (cCMV) infection is one of the most common intra-uterine viral infection (3). It is the leading cause of non-genetic sensorineural hearing loss (SNLH) and is an important cause of neurodevelopmental disabilities in children (4).

Cytomegalovirus is a member of the Herpesviridae family. There are 11 species in the genus cytomegalovirus; human betaherpesvirus 5 (HCMV, human cytomegalovirus, HHV-5) (5) is the species which infects humans, transmission depends on humans coming in contact with bodily fluids of an infected patient (6). Like all the other herpes viruses once a person gets infected with CMV, the viral infection remains lifelong, herpes viruses have the ability to remain latent for a long period of time. Many people have CMV infection without even realising it since it rarely causes any problems in healthy people; it is mostly found latent but can sometimes be reactivated.

Manifestations of the virus mostly arise in newborns who were infected in utero (cCMV), during birth or shortly after. CMV infection can cause significant morbidity and mortality in patients who have a weakened immune system such as pharmacologically immunosuppressed transplant patients and patients with AIDS (1,10, 11). Symptomatic cCMV most commonly occurs when the mother contracts the virus for the first time during pregnancy and is referred to as primary maternal infection. The mother then transmits the virus to the fetus in utero through the placenta which then replicates in multiple embryonic or foetal tissues (9). In the foetus, CMV infection commonly affects the foetal brain and the auditory system. Viral-induced damage often occurs in the bilateral subventricular zone (SVZ) where neural progenitors/stem cells are the predominant cell type. The exact mechanism by which CMV affects this zone remains unclear (10). Non- primary CMV infection occurs when mothers have pre-existing antibodies to CMV either due to the contraction of a different viral strain or by the reactivation of a previous maternal infection (11)

Risk of trans-placental transmission of a primary maternal infection is as high as 35% of which only around 15% are born symptomatic, hence this makes the disease difficult to detect. (12,13,14). Primary CMV infections are associated with the greatest risk of in utero- transmission when compared to non-primary infection in utero transmission rate (15). Vertical transmission rate increases in mothers with older gestational age at infection (15,16). If foetal infection occurs in the first half of the pregnancy the foetus has a higher risk of developing more adverse effects. In populations having high maternal seroimmunity, most cases of cCMV are due to non-primary infection, they have high rates of congenital

infections even though primary maternal infections have a higher rate of transplacental transmission to the foetus (17,18). The exact mechanism by which CMV causes infection and malformations in the developing foetus is still largely unknown.

Transmission of the virus to the pregnant mother is either through direct contact with people or indirectly through contact with infectious bodily fluids such as urine, blood, saliva, breast milk, semen and cervical or vaginal secretions. The main sources of maternal infection is through contact with young children who are asymptomatically shedding CMV and or through sexual activity (11,19,20).

SYMPTOMS IN ADULTS

Maternal CMV infection very often goes undetected since in 75% to 95% of mothers are asymptomatic (9). Symptoms of adult CMV infection are very similar to those caused by the Epstein-barre virus; these include malaise, fever, headache, pharyngitis, lymphadenopathy, hepatosplenomegaly, arthralgias and rash. In healthy individuals, CMV infection is usually self-limiting and enters in the lifelong latent phase within myeloid progenitor cells and peripheral monocytes. In some cases of immature, suppressed or compromised immune system severe disease can occur and can lead to permanent major sequelae or even death. Various studies have shown that even in immunocompetent patients, CMV can cause a wide range of manifestations most commonly involving the gastrointestinal tract such as colitis followed by central nervous system manifestations including encephalitis, meningitis, and myelitis. Haematological abnormalities such as anaemia and thrombocytopenia have been recorded. Other manifestations include liver, lung, vasculature, and eye disease (1).

SYMPTOMS IN NEONATES

Around 85% of babies that have acquired congenital CMV are asymptomatic and appear healthy at birth. Symptomatic cCMV infection carries a mortality risk of up to 7-12% in the period just after birth and increased morbidity risk due to neurodevelopmental delays as a result of central nervous system (CNS) damage, SNHL and visual impairment. Around 10 % of those who are asymptomatic still go on to develop long term neurological sequelae such as sensorineural hearing loss and therefore it is important that these children receive a series of audiological monitoring throughout their first years of life irrespective of their clinical presentation at birth to allow for early detection of possible SNHL (15,21).

Congenital CMV (cCMV) infection can give rise to various foetal malformations including, microcephaly, intracranial calcifications, echogenic bowel, intrauterine growth restriction, ascites, ventriculomegaly, lenticulostriate, pericardial effusion and hepatomegaly among others with the commonest presentations being premature birth, low birth weight, jaundice, petechiae, hepatosplenomegaly and microcephaly. Other signs include developmental delays and ophthalmological defects such as chorioretinitis with or without atrophy and cataracts which may be

associated with visual impairment. CCMV infection can also cause placental inflammation and seizures. Unfortunately, in 4% of symptomatic cCMV infected foetuses, death occurs in utero or shortly after birth (12,14,22,23,24,25). The earliest signs of congenital CMV infection may be seen on routine foetal ultrasound (9).

DIAGNOSIS OF CONGENITAL CMV

Unfortunately, congenital CMV infection often goes undetected at birth since most affected infants are asymptomatic or present with non-specific symptoms for which CMV is not suspected (4). Despite its health, economic and social burden, CMV screening programs for both pregnant women and new-borns are not yet implemented (15). At present, universal screenings for cCMV infections are not recommended due to the lack of effective treatment and vaccines (26). Recently, many studies have shown that early detection and intervention with antiviral drugs can improve neurological outcomes in symptomatic newborns (26,27).

In cases of suspected infection due the presence of foetal abnormalities, maternal testing for CMV is recommended. Foetal abnormalities can be seen on ultrasound or MRI and include, intra-uterine growth retardation, intracranial calcifications, microcephaly, hepatosplenomegaly, and echogenic foetal bowels. However, these findings are not specific to CMV since these signs and symptoms could be due to other congenital infections or chromosomal abnormalities (11).

Serologic testing is used to diagnose maternal CMV infection and consists of measuring the presence of CMV-specific immunoglobulin G (CMV IgG) and CMV-specific immunoglobulin M (CMV IgM) from maternal blood. This indicates recent or prior infection. The gold standard for diagnosing primary maternal infection is the detection of CMV IgG seroconversion (26).

The presence of IgM alone usually indicates acute infection; however, IgM can persist for months following infection hence it can also be detected during the reactivation and reinfection stage. This serologic IgM assay has a high false positive rate and therefore, diagnosis of primary infection cannot be based solely on this. On the other hand, low IgG avidity is found to be both a specific and a sensitive marker of primary CMV infection (9,28) hence used as a confirmatory test to identify primary CMV (26).

Various studies have shown that polymerase chain reaction (PCR) assay for CMV DNA in the amniotic fluid is both sensitive and specific for the prenatal diagnosis of foetal CMV infection and hence it is the gold standard for prenatal diagnosis of foetal CMV infection. The test detects the virus, which was excreted through urine in the amniotic fluid. For this test to be of significance, foetal urination prior to amniocentesis needs to be established and therefore this test needs to be carried out after 20-21 weeks of gestation. The amniocentesis and PCR needs to be carried out at least 6 weeks after the primary maternal infection to reduce false negative results (26).

Even though there are many benefits of undergoing this test for diagnosis, the fact that this test is an invasive procedure makes it unrealistic for all pregnant women suspected of having primary CMV to undergo this test. This test should be used for targeted neonatal screening for CMV IgG and IgM positive pregnant women and not as a universal neonatal screening (26,29).

Possible universal screening tests to detect all newborns with congenital infection are PCR assays for CMV DNA in saliva or urine of newborns (26,29). This test however has some limitations since PCR assay of the newborn's saliva can give a false positive due to CMV shedding into the maternal breast milk; therefore, a confirmatory PCR assay of the urine is required.

Neonates who test positive for CMV should have a workup done including ophthalmoscopy, neurological and physical examinations, cerebral ultrasound, a head CT and MRI and an auditory brainstem response testing (26). Studies have shown that drugs such as intravenous ganciclovir and oral valganciclovir may improve neurological outcomes in symptomatic neonates (26,30,31).

PREVENTION OF CONGENITAL AND MATERNAL CMV INFECTION

To reduce the burden of congenital CMV infection it is important to implement strategies for early detection, treatment and prevention of maternal infection and mother to child transmission (MTCT) (32).

Education of pregnant women regarding mode of transmission and sources of exposure and behavioural intervention remains the mainstay of interventions for the prevention of maternal infection and ultimately congenital CMV. Good hygiene is the best prevention against CMV. Pregnant women and their partners are encouraged to practice frequent hand hygiene using soap and water especially if they are in contact with young children or items which are contaminated by their bodily fluids. It is recommended not to share food and utensils as these can spread CMV (15,33). Till this day there are no effective vaccine which prevents CMV transmission (34).

Various studies have shown that pre-existing immunity plays a relevant role in reducing the risk of transplacental CMV transmission and foetal infection, this forms the basis of CMV vaccine research studies (35). Currently, there are many ongoing clinical trials to try and find an effective vaccine to protect against CMV infection (32,36).

TREATMENT STRATEGIES FOR CONGENITAL CMV INFECTION

Despite it being the commonest congenital infection, so far, treatment options are limited due to insufficient evidence for effectiveness and safety (37). Consequently, antiviral therapy to treat congenital CMV is not recommended to be used routinely (38). Treatment is usually reserved for symptomatic infants; various studies have shown an improved developmental outcome and possible prevention of hearing loss when symptomatic infants with cCMV are given 6 months of oral valganciclovir therapy. This treatment does not reverse the damage that has already occurred and is recommended based on the severity of symptoms such as evidence of CNS disease, life-threatening disease, severe single organ, or multi-organ involvements (37,39). Other supportive measures such as blood products and platelet transfusions can be given in cases of thrombocytopenia and anaemia. Infants with asymptomatic CMV infection should not receive antiviral therapy but should be monitored and assessed for developmental delay and late onset hearing loss. Research for new antiviral drugs of good safety profile for combination therapy is ongoing (40). As the child grows, functional therapy such as physical therapy, occupational, speech/language and vision therapy may be needed. Children with hearing loss may be taught sign language, make use of hearing aids or undergo cochlear implant procedures.

CONCLUSION

Congenital CMV infection can lead to significant and permanent consequences in the infected foetus. Despite this, universal screening for both pregnant women and neonates is not yet recommended routinely due to the lack of safe and efficacious treatment regimes. Preventative strategies are still lacking and so a lot of emphasis is put on the importance of behavioural measures such as reduction or avoidance of contact with young children's bodily fluids such as saliva and urine and to practice frequent hand hygiene. Specific foetal diagnostic tests can be carried out in cases of high suspicion of congenital CMV since research has shown that early diagnosis and treatment improves hearing and developmental outcomes.

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Foetal Alcohol Spectrum Disorders and Imaging: A Brief Review

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Foetal Alcohol Spectrum Disorders (FASD) refers to the collection of features seen as a result of prenatal alcohol exposure by the mother. FASD can be considered as an acquired brain injury, predominantly affecting neurocognitive development, amongst other organ systems (1). An effected individual may not necessarily possess all the characteristic features of the syndrome, with varying degrees of severity being displayed (2).

EPIDEMIOLOGY & AETIOLOGY

A recent study concluded that 1 in 13 women who consume alcohol during pregnancy had a child with FASD (3). There is no safe amount of alcohol to drink during pregnancy. However, a daily alcohol consumption of four or more drinks during pregnancy significantly increased the risk of developing FASD (4). FASD is considered to be one of the commonest avoidable causes of intellectual disability (1). In fact, approximately 1700 neonates are born each day with FASD globally, with a higher incidence amongst the high-risk populations, such as incarcerated cohorts; children in care; aboriginal populations and those under psychiatric care. Incidence is highest in South Africa (111.1 per 1000 population); however, an accurate quantification of FASD is challenging due to under-diagnosis and confusion with other syndromes, such as autism spectrum disorder or ADHD (3,5).

Alcohol is a teratogen which freely crosses the placenta from the mother to the foetus. This leads to a blood alcohol content of the foetus which is higher or the same as that of the mother for longer periods, since the developing liver cannot effectively eliminate it due to low levels of foetal alcohol dehydrogenase. Cytochrome P450 2E1 is one of the major enzymes which catalyses ethanol oxidation in the liver. Reactive oxygen species may be generated from this reaction when improperly coordinated in the foetus, leading to lipid peroxidation as well as protein and DNA oxidation, with detrimental effects (6). Moreover, the epigenetic effects of alcohol have also been studied, with DNA methylation and histone modification, further adding to the complex aetiology of alcohol-related damage (7).

The risk of damage from alcohol exposure is highest during the first trimester, especially during gastrulation and folding. However, alcohol exposure can impact foetal development at any point in the pregnancy (8).

DIAGNOSIS & CLASSIFICATION

Diagnosis of FASD can be challenging, given the variety of the phenotype. The basic diagnosis is made upon a positive history of prenatal alcohol exposure and the presence of severe impairment in at least three of the ten neurodevelopmental domains, listed below (9):

- Brain structure
- Motor skills
- Cognition
- Language skills
- Academic achievement
- Memory
- Attention
- Executive function, including impulse control and hyperactivity
- Affect regulation
- Adaptive behaviour, including social communication and skills

Moreover, there are four distinct sub-types of the spectrum (2):

- Foetal alcohol syndrome (FAS)
- Partial foetal alcohol syndrome
- Alcohol-related neurodevelopmental defects
- Alcohol-related birth defects

Foetal alcohol syndrome is the most severe form of FASD, with significant deficits in motor skills; cognition; memory and behaviour. Growth retardation is also a common feature. 'Partial foetal alcohol syndrome' is a diagnosis reserved for children with a confirmed history of alcohol exposure but do not display all the features of FAS and is typically milder. 'Alcohol-related neurodevelopmental defects' refers to children with behavioural and learning issues associated with prenatal alcohol exposure. Finally, 'alcohol-related birth defects' is when a neonate is born with organ damage related to alcohol (10). Figure 1 provides the diagnostic algorithm by which FASD can be accurately diagnosed.

Sentinel facial features refer to the characteristic appearance that individuals suffering from FASD possess (1). These include:

- Short palpebral fissures
- Smooth philtrum
- Thin upper lip
- Epicanthal folds
- Flat nasal bridge
- Micrognathia

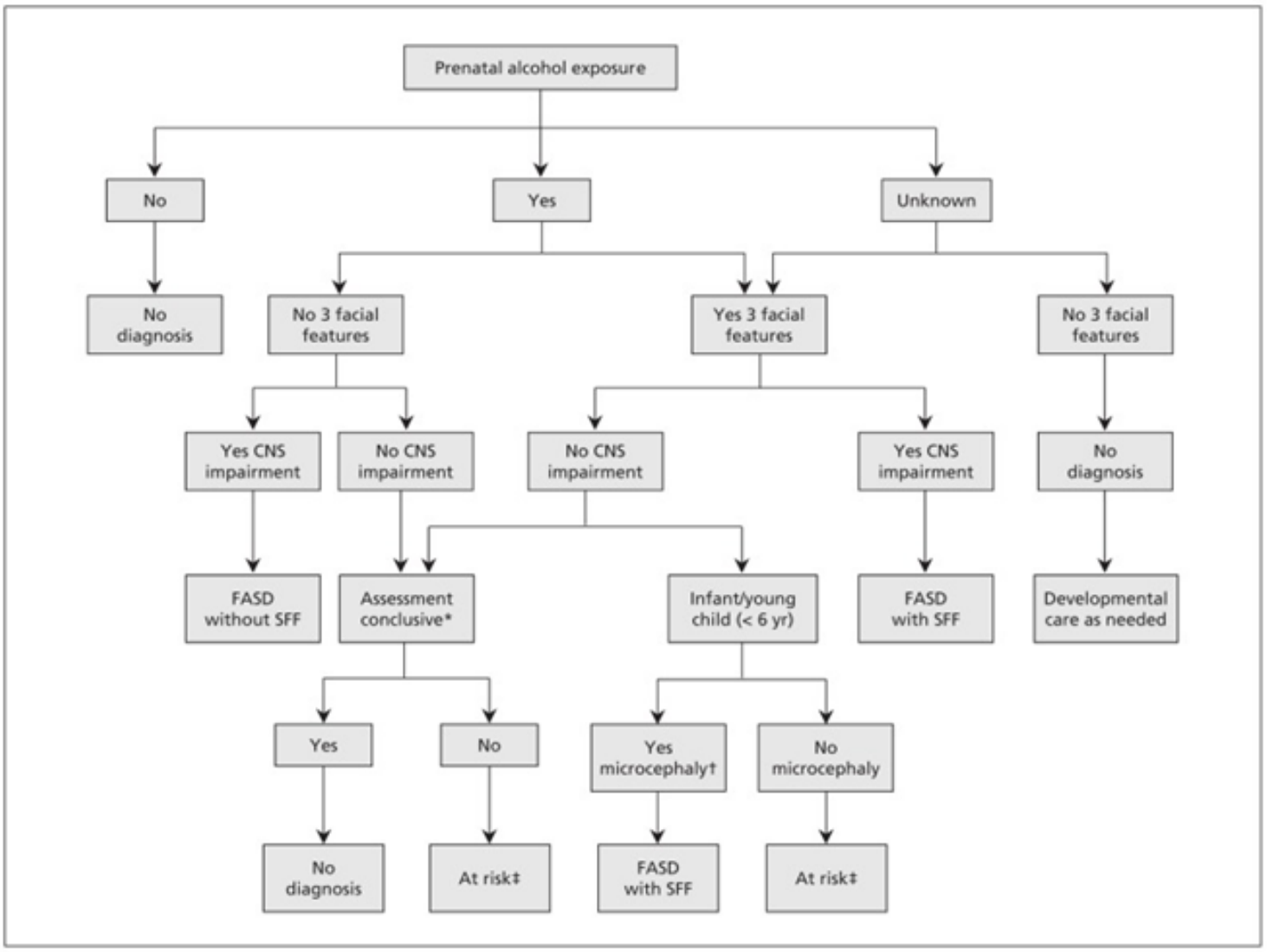

Figure 1: *FASD Diagnostic Algorithm. CNS involvement refers to impairment in 3 or more developmental domains. SFF – sentinel facial features. Obtained from: (23)*

PRENATAL DETECTION WITH ULTRASOUND

Ultrasound can lead to an early diagnosis of FASD in utero, allowing for more comprehensive interventions to be carried out. Detection may be subtle, especially in mild cases. However, since expectant mothers routinely undergo such ultrasound scans as part of antenatal care, it may be useful to implement FASD screening during such scans, especially in high-risk populations. Two questionnaires are routinely used to identify mothers at risk of drinking, namely the TWEAK tool (tolerance, worried, eye-opener, amnesia, cut-down) and the AUDIT tool (Alcohol Use Disorders Identification Test), (11,12).

A number of sonographic biomarkers visible during the second and third trimesters can be affected with prenatal alcohol exposure. These involve measurements of the conceptus, which are then compared to the normal reference measurements, and include the following (11,12):

- Transverse cerebellar diameter (TCD);
- Outer orbital diameter (OOD);
- Occipital-frontal diameter;
- Fronto-thalamic distance (FTD) – the distance between the internal aspect of the frontal bone and the posterior aspect of the thalami;
- Interorbital distance (IOD);
- Caval-calvarial distance (CCD) – the distance between the internal aspect of the frontal bone and the posterior margin of the septum pellucidum;
- Orbital diameter (OD);
- Reduced biparietal diameter and femur length – reflecting intrauterine growth restriction.

Once detected on scanning, efforts should be made to stop any further alcohol intake by the mother. Prenatal nutritional changes may help mitigate some of the effects of alcohol. In rodent models, a diet rich in antioxidants (i.e., vitamin A, vitamin E and omega 3 fatty acids) has been shown to lead to offspring with less oxidative stress and behavioural issues (7). However, further research must first be performed in order to conclusively apply this to humans. The same study also found that exercise in the affected individual may improve learning, coordination and memory (7).

Upon birth and clinical confirmation of the diagnosis, initiation of early intervention services may occur. These typically include special education; frequent check-ups and behavioural therapies. If warranted, parent training and/or relocation of the child into a more stable household may be done for the child's best interest. No treatment or cure is currently available for FASD; however the symptomology may be treated, using a combination of neuroleptics, stimulants and anxiolytics (13).

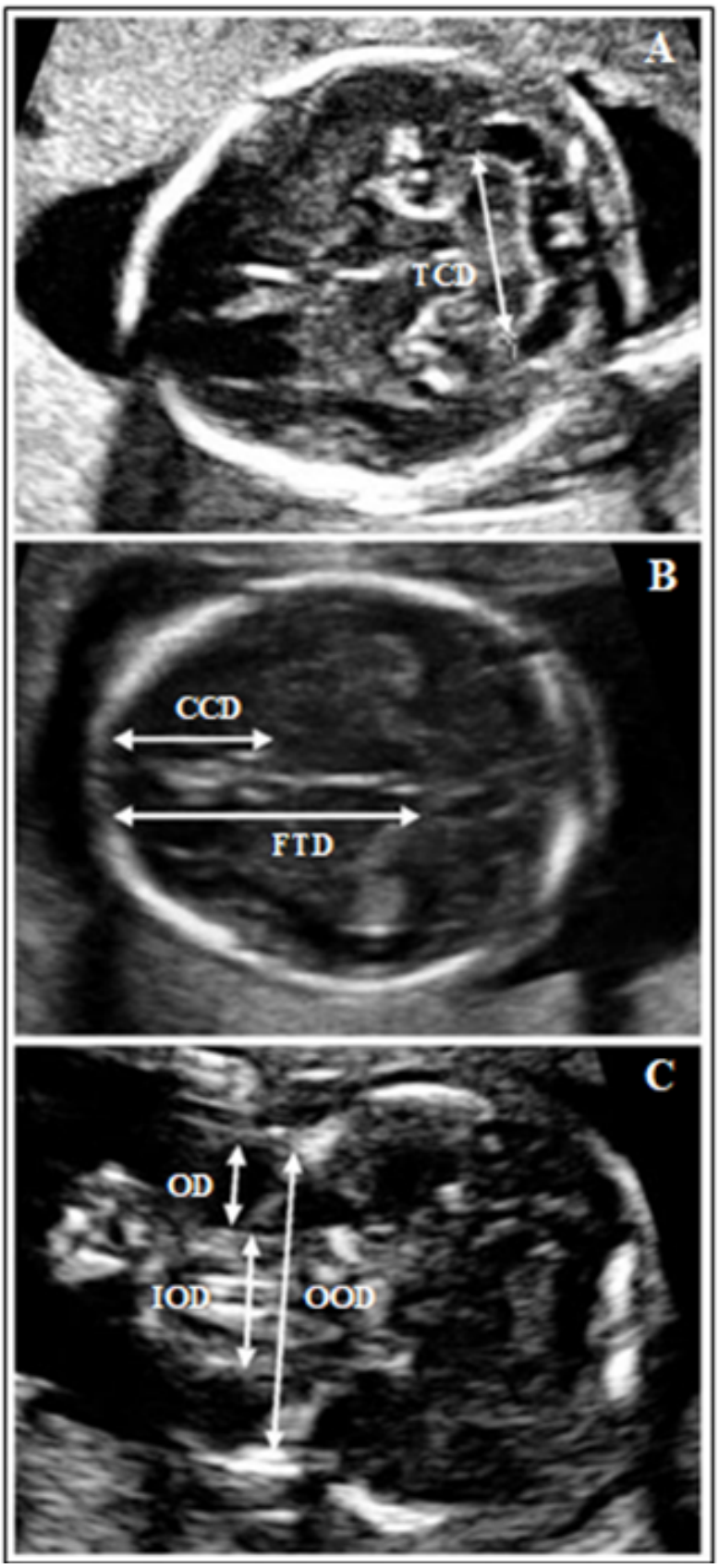

***Figure 2**: Prenatal ultrasound showing axial view of the calvaria with markers annotated. Obtained from: (11)*

NEUROIMAGING IN FASD

Although the diagnosis of FASD is mainly clinical, using the history and phenotype, radiological imaging in the context of FASD may aid in confirming the diagnosis (since some cases may be non-dysmorphic); assessing severity; evaluating associated comorbidities and deciding on appropriate management (14).

Imaging of the affected individual's brain is primarily done using Magnetic Resonance Imaging (MRI), allowing for excellent soft tissue definition without any exposure of infants and children to ionising radiation, as opposed to Computed Tomography (CT).

MRI studies typically reveal a generalised reduction of cerebral volume (i.e., microcephaly). Several studies have also noted that specific sites are especially affected by prenatal alcohol exposure, namely the corpus callosum; the frontal and parietal lobes; hippocampus; caudate nucleus and the cerebellar vermis (15). This may indicate that certain regions of the brain are more susceptible to alcohol-related damage (14). These changes are what lead to the neurocognitive impairments, and their extent depends on which brain regions are most affected. For example, anomalies in the frontoparietal lobes are consistent with the difficulties in planning and spatial memory commonly seen in FASD cases.

In severe cases, white matter hypoplasia may be observed on MRI, especially in the perisylvian and parietal regions on the brain. Such defects are best demonstrated with diffusion tensor imaging, a novel MRI technique which shows the white matter axonal pathways. Conversely, an increase in the grey matter density may be seen in the inferior parietal and superior temporal lobes (14).

In fact, through animal models and post-mortems done on confirmed FASD cases, it has been observed that dendritic arborisation is disrupted, with the resulting neurons having dendrites which are short and lack branches. Furthermore, while alcohol seems to inhibit all stages of brain development, the exception is neuronal apoptosis, which is increased due to the reduced stimulation by neurotrophins (16). Finally, alcohol suppresses the excitatory neurotransmitter glutamate and enhances the release of GABA, which exerts an inhibitory effect (17).

Other imaging modalities used to study the living brain include functional MRI (fMRI), which provides a better idea of how the individuals' brain processes information. This is done by measuring blood flow to the different parts of the brain following control questions. A recent study managed to demonstrate the working memory deficits in FASD patients on fMRI (18). Positron emission tomography (PET-CT) scanning provides insights into the metabolism of the brain; however, both fMRI and PET-CT scanning are typically reserved for research into FASD. Interestingly, multiple anomalies are found more frequently in older individuals (19).

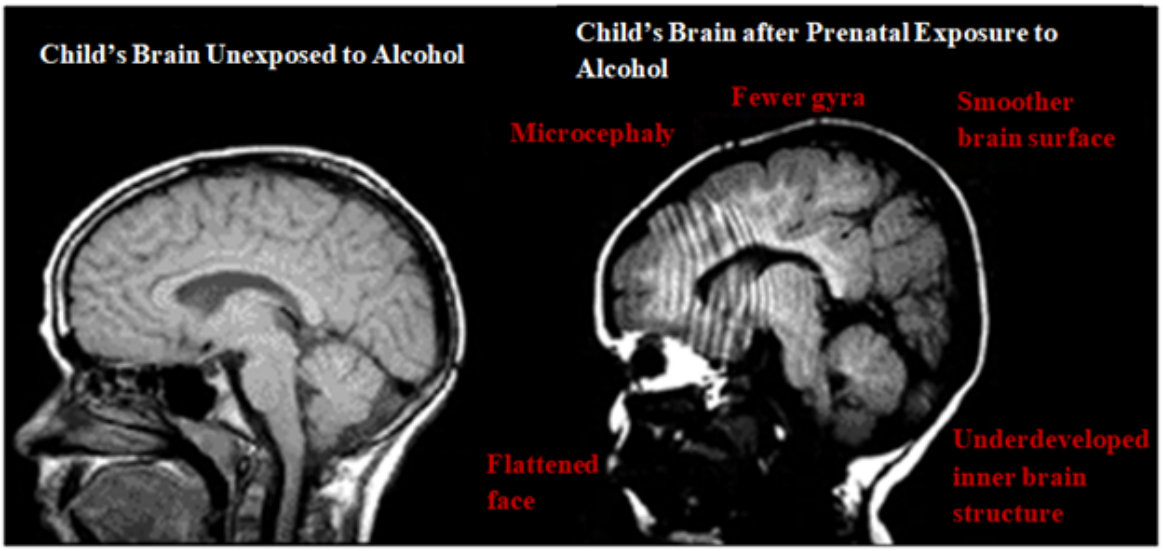

Figure 3: *Sagittal T1-weighted MRI of a healthy child and that of a child diagnosed with FASD. Obtained from: (22)*

OTHER ORGAN SYSTEMS AND IMAGING

Whilst the brain is the main affected organ, a number of associated features may be present in this disorder. These may be examined using several imaging modalities, depending on the site.

Acetaldehyde is a product of ethanol metabolism, which when in excess inhibits the formation of retinoic acid from retinol. Retinoic acid plays a key role in the proliferation and differentiation of cardiac progenitor cells, resulting in cardiac abnormalities in patients with FASD. Mainly, these include atrial or ventricular septal defects and atrioventricular valve defects (20). Such defects can be adequately visualised using echocardiography or cardiac CT when suspected.

Musculoskeletal defects are also common in FASD, and severe prenatal alcohol exposure may give rise to foetal alcohol myopathy; growth restriction and abnormalities in the neuromuscular junctions, which may possibly impair locomotion and cause hypotonia. Furthermore, the metabolism of glucose by skeletal muscle may be altered, causing glucose intolerance and insulin resistance. This in part contributes to the increased risk for individuals with FASD to develop type 2 diabetes (21). Other skeletal problems which may be encountered include radio-ulnar synostoses, pectus excavatum and congenital scoliosis (1). Ultrasound and MRI may be used to examine and skeletal muscle defects, while CT and planar x-rays may be used to evaluate any bony anomalies.

CONCLUSION

FASD is a complex and multifaceted disorder involving multiple organs. Radiological imaging, both antenatally and postnatally may assist in the diagnosis and management of the disorder, with the aim of ameliorating the individual's quality-of-life.

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Polycystic Ovaries Syndrome and its Impact on Fertility

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DIAGNOSING PCOS

Widely referred to as the thief of womanhood, polycystic ovary syndrome (PCOS)- also known as Stein Leventhal syndrome is a significant public health issue, manifesting reproductive struggles in 8-13% of gynaecological aged woman (1-4). Educating the public by raising awareness is pivotal when managing this condition. In fact, although it may be common knowledge that PCOS affects a woman's fertility, perhaps only a small minority are aware of the triadic nature of this condition thus neglecting the accompanying endocrine (5,6) and psychological (7-9) ramifications. In essence it is the amalgamation of these three pillars which is responsible for the deeply stigmatizing symptomatology characteristic of PCOS. This eventually culminates in affected women perceiving themselves as being less feminine than their peers (10).

THE DIAGNOSTIC ROTTERDAM CRITERIA

Two out of three of the following conditions must be met for PCOS to be diagnosed (11):

1. Ovulatory dysfunction with or without oligomenorrhea
2. Biochemical hyperandrogenism
3. Polycystic ovaries morphology

In some instances, despite women presenting with characteristics of PCOS, these do not match the mentioned diagnostic criteria. Physiological acclimatization of the hypothalamic, pituitary and ovarian axis occurs 8 years post-menarche (12). This means that only at this point can one confidently determine the female's baseline and hence assess for menstrual regularity and ovarian morphology.

This, coupled with the psychological burden imparted by the diagnosis, emphasizes the importance of delaying PCOS diagnosis in reproductively immature females, and to instead consider them as candidates for reassessment due to increased risk. Diagnosis optimization also requires judicious use of combined oral contraception so that this is ideally only prescribed once the patient has reached reproductive maturity, thus preventing delayed presentations and over-treatment.

1) IRREGULAR CYCLES AND OVULATORY DYSFUNCTION

According to the European Society of Human Reproduction and Embryology (ESHRE), a female is said to have an irregular period if: -

- Menarche has not occurred by age 15
- Despite no menarche, more than three years have passed since breast development.
- The female is 1-3 years post-menarche with the menstrual cycle averaging less than 21 days or greater than 45 days.
- The female who is more than one year post menarche has had any single cycle lasting more than 90 days.

The female is 3 years post-menarche and experiences less than 8 cycles per year/ cycles less than 21 days/cycles longer than 35 days.

1) IRREGULAR CYCLES AND OVULATORY DYSFUNCTION

Delving into the pathophysiology of PCOS is essential for understanding the remaining two pillars of the Rotterdam Criteria.

Female fertility is governed by the hypothalamic- pituitary- ovarian axis. In physiologically fertile women there is the fluctuating pulsatile release of gonadotropin releasing hormone (GnRH) from the hypothalamus. High pulse frequency brings about the release of luteinizing hormone (LH) whilst low pulse frequency stimulates follicle stimulating hormone (FSH) release from the anterior pituitary gland (13). At this point it is paramount to understand that the correct FSH:LH ratio is essential for ovulation to occur.

FSH and LH act on the granulosa cells (14) and thecal cells (15) of the meiotically arrested follicles respectively. Whilst both of them appear to be synergistic in terms of follicular development, as the name implies FSH has a much stronger and pronounced effect. In essence a number of follicles will start to mature per cycle, but only one of them will complete its lifecycle to give the mature graafian follicle. This process encompasses the first half of the female menstrual cycle – the follicular phase.

Around 36 hours prior to ovulation, LH becomes the predominant hormone, so that the surge in its level brings about the release of the oocyte from the graafian follicle. This is ovulation and signals the onset of the second part of the menstrual cycle (the luteal phase) which is maintained by the remains of the graafian follicle which form the corpus luteum (16).

As discussed, in PCOS, the female has anovulatory cycles, this evidently means that no corpus luteum forms and therefore the menstrual cycle is dominated by the follicular phase.

The result is deranged oestrogen and progesterone levels. Oestrogen is high due to the high number of non-ovulating follicles, whereas progesterone is low as no corpus luteum is formed. Normally progesterone brings about negative feedback at the level of the hypothalamus so as to decrease the pulse frequency of GnRH, this is lost in PCOS. This causes an increase in the LH FSH ratio since the LH secreting cells are more responsive to the increased pulse frequency (17).

Furthermore, the high oestrogen level brings about a feedback loop at the level of the anterior pituitary which suppresses FSH release but enhances LH release. Coupling of these phenomena results in significant derangement of the normal FSH:LH ratio the pinnacle of which gives rise to the PCOM described in the Rotterdam Criteria.

PCOM requires the presence of at least one of the following (18): -

i) 25 or more follicles in one or both ovaries each with a size of 2-9mm each.

ii) An ovarian volume equal to or greater than 10ml as a result of these atretic follicles.

The term PCOS is a misnomer as the 'cysts' are actually atretic follicles (12) i.e previously responsive and maturing follicles which following biochemical influences exhibit arrested maturation and subsequent degeneration leading to an-ovulation (19-20).

Detection of PCOM requires the use of ultrasound, which ideally in the sexually active female utilizes an endovaginal probe. It is important to note that different cut off points are used for diagnosis depending on the frequency of the utilized probe. Textbook PCOM presents with the pathognomonic 'string of pearls' sign due to the peripheral distribution of the mentioned follicles (20).

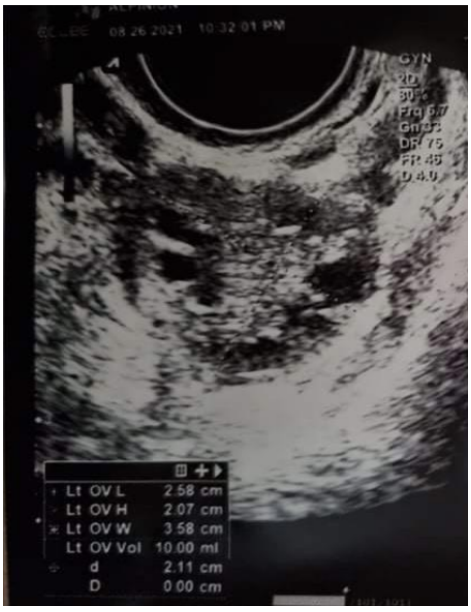

***Figure 1**: Ultrasound image exemplifying the characteristic string of pearls sign seen in PCOS*

It is worth mentioning that in females with a gynaecological age less than 8 years, ultrasound is not to be used for diagnosis due to the high incidence of multi-follicular ovaries. Also, transabdominal ultrasound is not accurate in terms of ovarian volume determination (12).

2) BIOCHEMICAL/CLINICAL HYPERANDROGENISM

Elevated levels of free testosterone and increased free androgen index are the hallmark of PCOS (21) affecting between 60-100 % (12) of diagnosed patients. Whilst increased levels of androsteindione and DHEA are seen in 18% (22) and 25% (23) of PCOS women respectively, the Rotterdam consensus holds that the most accurate biochemical test remains the free androgen index (24-25).

Androgen upregulation is attributed to the abnormal folliculogenesis (26), which as discussed is as a result of neuroendocrine dysregulation. The tandem effect of increased LH and decreased FSH enhances steroidogenesis through hyperplastic changes occurring at the level of the theca interna cells (21). In addition, polymorphisms in the CYP gene family governing steroid metabolism have also been implicated. Decrease levels of steroid hormone binding globulin are also evident and result in increased levels of unbound, active testosterone.

Clinical symptoms and signs of hirsutism, acne and androgenic alopecia occur secondary to the androgen's effects on peripheral tissue (21). Since biochemical investigations may be costly standardized universal visual modalities of assessing said clinical manifestations have been developed.

HIRSUTISM

This is the commonest and most reliable symptom (21) of hyperandrogenism, found in 60-80% of PCOS women (27-30). Hirsutism refers to the presence and masculine distribution of pigmented, medullated hair which if left unpampered grows more than 5mm in length (31). Hirsutism over estimation requires villus hair to be distinguished from the defined terminal hair.

The visual scoring tool utilized is the modified Ferriman-Gallwey score with scores of 8 or more being diagnostic of Hirsutism (32,33) .

ACNE VULGARIS

Although there is no universally accepted visual assessment tool for this (34), acne on the face, upper back, neck and pectoral regions remains the second commonest sign of hyperandrogenism (21), with an incidence of 9- 34% (35,36).

Like in the case of Hirsutism the increased free testosterone result in amplified amounts of the more

potent dihydrostosterone which acts on the pilosebaceous glands to increase sebum production and abnormal desquamation of follicular epithelial cells. The result is an increased susceptibility to Propionibacterium colonization (21).

ANDROGENIC ALOPECIA

Whilst hirsutism results in increased hair growth, the increased testosterone also results in thinning of scalp hair. Hair is lost from a triangular patch extending from the anterior mid vertex to the crown of the head in a posterolateral fashion sparing the anterior hair line. This is male pattern balding and is seen in 3.2-34.8% of PCOS women (22). The Ludwig visual Scale is utilized for diagnosis (34).

PCOS PHENOTYPES

Diagnosing PCOS is controversial due to heterogeneity in patient profile, in fact four PCOS phenotypes have been defined (37).

Phenotype A: Incidence of: 67.7% making it the commonest type. Androgen excess + Oligomenorrhea+ PCOM.
Phenotype B: Incidence: 11% Androgen excess+ Oligomenorrhea.
Phenotype C: Incidence: 17.7% Androgen excess+ PCOM
Phenotype D: Incidence: 3.6% making it the rarest Oligomenorrhea + PCOM

LONG TERM CONSEQUENCES OF PCOS AND TREATMENT

In PCOS, there is a deranged endocrine status resulting in a number of metabolic sequelae and hence co-morbidities. In fact, one may postulate that the term PCOS is a misnomer, and that instead the term ‘Female Metabolic Syndrome’ should be utilized.

Although pharmacological treatment is both available and effective, simple conservative measures such as prevention of weight gain or weight loss in patients with a BMI greater than 25kg/m2 may prove as efficacious as drug therapy by combating any hyperinsulinemia and insulin resistance(38-40).

INSULIN RESISTANCE, IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES MELLITUS

PCOS is a non-modifiable risk factor for type II diabetes mellitus (T2DM) so that it is seen in 65-80% of patients (40) 41. In PCOS, there are high levels of circulating insulin which stimulates thecal cell and

adrenal cortex steroidogenesis (42,43) 42 43. This increases hyperandrogenism and worsens LH:FSH ratios hence aggravating reproductive and metabolic features (44,45).

Appropriate management of T2DM improves PCOS, as a result it is essential to screen such patients with an HbA1c test, or more accurately using an oral glucose tolerance test.

CARDIOVASCULAR RISK

High insulin and androgen levels decrease the production of serum hormone binding globulin (SHBG) which contributes to the early onset of cardiac events (46). Dyslipidaemia and hypertension also seem to be part and parcel of PCOS.

The risk for each patient should be calculated to guide treatment. Although not recommended, studies have shown that use of statins improve not only the metabolic profile but also the hyperandrogenism (47,48).

INFERTILITY

Infertility refers to a couple who has been unable to conceive after 6-12 months of unprotected sexual intercourse (49).

This may be either directly due to the anovulatory cycles or secondary to other PCOS implications namely endometrial cancer

ENDOMETRIAL CANCER

Due to the follicles being ‘stuck’ in the follicular phase, the endometrial lining, under the effect of oestrogen and in the absence of progesterone continues to proliferate. This turns pathological whenever there is an endometrial thickness of 7mm or more, this is endometrial hyperplasia (50,51) and is associated with a 2.89 fold increased risk for endometrial cancer (52).

It is advisable for these oligomenorrheic women to undergo a withdrawal bleed every 3-4 months to prevent this transformation. Treatment involves the use of gestogens for 12 days (53). These can be either the progesterone only pill, the combined oral contraceptive pill or gestogen devices such as the Mirena (54)

ANOVULATORY INFERTILITY

In PCOS there is no oocyte release so it follows that the subsequent stages of fertilization and embryo development will not occur.

Treatment for patients who are not looking to conceive involves the initiation of the combined oral contraceptive pill with or without the use of the insulin sensitizing agent metformin (55-59). Interestingly enough metformin can also be used as an ovulation induction agent (60).

Patients who are looking to conceive may undergo either ovulation induction centered therapy or in vitro fertilization (IVF)

OVULATION INDUCTION THERAPY

The first line agent for ovulation induction is an aromatase inhibitor known as letrozole (61,62). This enhances follicular maturation by increasing FSH secretion (63). Another ovulation induction agent is clomiphene citrate, which in itself is a selective oestrogen receptor modulator and therefore functions as both an oestrogen and anti-oestrogen (64). This influences the endometrium and cervical mucus which explains the discrepancies noted between good ovulation rates and pregnancy rates (65).

Letrozole use has superseded clomiphene citrate use due to a better side effect profile characterized by considerably less hot flashes. More importantly Letrozole increases the likelihood of live birth by 40-60% compared to clomiphene citrate and also reduces the risk of multiple pregnancies (66,67)

GONADOTROPINS

These include FSH and LH and are used as second line agents. Careful monitoring of follicular development via ultrasound is essential to prevent multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) (68,69) . In fact, the Gonadotropin inducing ovulation known as the trigger shot- is only given when there are 2 or less follicles over 14 mm (70).

LAPAROSCOPIC OVARIAN STIMULATION

Laparoscopic ovarian interventions via electrocautery, multiple ovary biopsies or laser vapor have been shown to resolve anovulation and normalize androgens and SHGB levels in 60% of patients for up to 20 years following the procedure in (71). However laparoscopic ovarian drilling is only suitable for women with a normal BMI(71).

IN VITRO FERTILISATION

IVF is a 5-step procedure, used as a third line treatment option in PCOS induced infertility.

IVF is a lengthy and costly procedure involving the use of multiple agents such as, gonadotrophins to enhance follicular development, GnRH antagonists to avert LH surge and hence premature follicular rupture and an HCG ‘trigger shot’ once ultrasonography detects follicular maturation (72,73).

The resultant oocytes are then harvested and exposed to male gametes, in some instances of male infertility intracytoplasmic sperm injection may need to be employed (72).

(72) with the developing embryo being implanted at the blastocyst stage (day 5) so as to prevent multiple pregnancies and increase live birth rates (72,74).The administration of Progesterone throughout the IVF cycle is essential to support and maintain pregnancy (72).

In certain instances IVF may propagate ovarian hyperstimulation syndrome (OHSS) which causes third space fluid shifts(75). This may result in hypovolaemia which may lead to acute kidney injury and thromboembolism (76). In order to prevent such sequelae, GnRH antagonists are preferred over GnRH agonists (75). Furthermore, prophylactic albumin may be administered.

PCOS AND PREGNANCY

It is pertinent to recognize that ones battle with PCOS does not end with conception and that thus tentative follow up of pregnant PCOS women is necessary (77). This is because PCOS can significantly complicate pregnancy and in fact places babies born to these women at an increased risk of requiring intensive neonatal care unit admission(78).

THE FOLLOWING ARE PCOS RELATED PREGNANCY PROBLEMS

Miscarriage

Pcos women have a three fold increased risk of miscarriage in the first trimester as compared to non pcos women. (79). This increased risk has been attributed to hyperinsulinaemia, insulin resistance, elevated LH levels, obesity and endometrial dysfunction (77). Some researchers also postulate that these factors may contribute to miscarriage by reducing ova quality(77).

Gestational diabetes

Early recognition of pregnancy-induced diabetes is imperative as it is completely treatable, however if this is not done promptly there will be significant foetal and maternal sequelae. Such infants will exhibit hypoglycemia ,respiratory distress (secondary to meconium aspiration) and macrosomia(80). Macrosomia is attributed to impaired foetal programming which arises from abnormalities in maternal glycemic control . This result in increased amounts of glucose crossing over to the foetus and hence metabolic abnormalities which culminates in infants that are larger for gestational age. Macrosomia in itself necessitates surgical delivery via C-section which in itself is associated with a number of complications as compared to natural vaginal delivery. In addition both the mother and the child are at an increased risk of developing type 2 diabetes mellitus later on in life(80).

Small for gestational age

Interestingly enough, in certain instances the hyperinsulinaemia and insulin resistance may conversely result in insulin dependent growth dysfunction so that PCOS patients are 2.5 times more likely to give birth to small for gestational age children as compared to healthy women(77).

Pre-eclampsia

As discussed, PCOS makes patients more susceptible to cardiac events. In fact, pcos women are at a 4 fold increased risk of developing pregnancy induced hypertension which is postulated to arise mainly from the increased arterial wall stiffness (81). It therefore follows that the blood pressure dysregulation makes it more likely for the blood pressure values to increase to destructive unchecked levels and hence concomitant renal, hepatic or cerebral problems. This is pre- eclampsia(79).

Furthermore, if the necessary precautions are not taken, the situation deteriorates further so that cerebral involvement presents as seizures and or coma, this is eclampsia. It therefore goes without saying that this is potentially fatal for both mother and foetus.

The definite treatment for this is emergency C-section delivery which is associated with increased risks, particularly if this scenario occurs before 37 weeks gestational as this by definition would result in premature delivery, which in itself presents health challenges right after birth and later on in life (79)

HEALTH OPTIMIZATION IN THE PREGNANT PCOS PATIENT

As a result of these issues pcos patients require special obstetric care mainly centered around normalization of BMI through lifestyle changes. Normalization of BMI in obese patients is pivotal as its value is reflective of hyperinsulinaemia, insulin resistance and dyslipidaemia all of which contribute to the increased morbidity and mortality during gestation (82,83).

The use of insulin sensitizing agents such as metformin throughout pregnancy is debatable as current studies do not concur with the actual therapeutic role of this agent in terms of minimizing pregnancy pathologies (77). Consequently, future research should focus on whether treatment with such agents can prevent or reduce the mentioned risks.

THE WAY FORWARD

Further studies should be focused on the therapeutic role of insulin sensitizing agents in PCOS particularly preparations of the secondary messenger inositol (76). Such medication has in fact been

found to improve hormonal, metabolic and reproductive profiles in PCOS patients by normalizing the ratio between the two inositol isomers: myoinositol (MI) and Dchiroinositol (DCI).

In addition, the safety profile of IVF should also be optimized though the use of in vitro maturation (IVM). This involves harvesting unstimulated or mildly stimulated oocytes in the laboratory, thus virtually eliminating the risk of OHSS (84,85).

CONCLUSION

PCOS is a common pathology, requiring medical support throughout the female's lifecycle due to its multifaceted pathogenesis.

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Psychiatric and Dermatological Conditions during Pregnancy

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During pregnancy, the female body undergoes various different changes, both physical and psychological. It is important to raise awareness about certain conditions which may be of concern to a pregnant mother. Psychiatric and dermatological conditions are both important aspects that may greatly affect the mother throughout and after pregnancy.

PSYCHIATRIC CONDITIONS

Pregnancy is usually associated with being a happy time full of positive emotions, however various women experience psychiatric conditions during pregnancy such as depression, anxiety disorders, and bipolar disorder (1). Unfortunately such conditions tend to be underdiagnosed and undertreated in pregnancy, as the psychiatric changes are blamed on physiological changes due to pregnancy, or doctors being unwilling to prescribe medication due to potential harmful side effects (2).

Depression

Depression is the most common psychiatric disorder associated with pregnancy (1). Symptoms of depression during pregnancy may be sometimes difficult to differentiate from the normal experiences of pregnancy such as changes in sleep, appetite and energy. Up to 70% of women report negative mood symptoms during pregnancy (3), however the prevalence rate of pregnant women with depression is around 15% (4).

There are various risk factors which may contribute to the development of depression during pregnancy, such as a past medical history of depression, stopping medication for previously diagnosed depression, a past history of postpartum depression, and a family history of depression. There are also important psychosocial factors which have been associated with depression during pregnancy, including a pessimistic outlook for the pregnancy, lack of social support, maternal stress due to negative life events, and a partner or family member being unhappy about the pregnancy (2).

Untreated depression in pregnancy can have dire consequences, such as inadequate prenatal care, substandard nutrition and self-care, substance abuse and self medication, suicidal thoughts and thoughts of causing harm towards the foetus, and may even lead to postpartum depression after the baby is born. Studies have also shown that maternal depression could also be linked to early childhood problems due to the psychological effect that the mother's depression may have on the foetus (5).

Treatment for depression in pregnancy is based on the same therapies used for depression along with the additional care for the safety of the foetus. Psychotherapies such as cognitive behavioural therapy and interpersonal psychotherapy have been found to be effective treatments for depression (6). Pharmacotherapies may also be used, however the risk and benefits need to be considered before starting treatment. The importance of education and support for a pregnant mother remain crucial, as women experience pregnancy differently, and in some cases may not be sure about what to expect.

Anxiety disorders

Anxiety disorders are another psychiatric complication that may affect pregnant women. Maternal anxiety may also cause negative consequences such as miscarriage, pre-eclampsia, pre-term delivery, and low birth weight. There is also a strong association between prenatal anxiety and the development of postpartum depression, even if prenatal depression is controlled (7). Some women may experience first-onset panic disorder or obsessive compulsive disorder during pregnancy, which may severely affect the mother's life and will therefore require treatment.

Psychosis

The risk of psychosis during pregnancy is not increased, unless prophylactic medication for previously diagnosed psychosis is stopped due to potential teratogenic effects. In fact, new-onset psychosis whilst pregnant is extremely rare. Notwithstanding this, in mothers with a past medical history of psychosis, the relapse rates of developing psychosis are high. The most common manifestations of psychosis during pregnancy are bipolar illness, psychotic depression and schizophrenia (2). Diligent monitoring of such psychiatric conditions during pregnancy is crucial. Psychosis during pregnancy can have disastrous effects including inadequate prenatal care, negative pregnancy outcomes such as low birth weight and prematurity, and neonaticide or suicide. It is therefore crucial to treat acute psychosis in pregnancy, and hospitalization may even be considered should the mother be assessed to be at risk of harming herself or her foetus.

DERMATOLOGICAL CONDITIONS

Skin problems are common during pregnancy, but accurate diagnosis of such conditions can be difficult. Common dermatological conditions during pregnancy can be generally divided into three categories: (1) Benign skin conditions due to hormone related changes, (2) Pre-existing skin conditions, (3) Pregnancy specific skin conditions.

(1) Benign skin conditions due to hormone related changes

Normal physiological hormonal changes may cause benign skin conditions such as striae gravidarum; hyperpigmentation; and hair, nail, and vascular changes.

Striae gravidarum (stretch marks) are extremely common in pregnancy, occurring in up to 90% of pregnant women by the third trimester (8). Striae appear as pink-purple, atrophic lines or bands that develop on the abdomen, buttocks, breasts, thighs, or arms. They are seen more often in younger women, women with larger babies, and women with higher body mass indices. Non-white women and women with previous striae or a family history of striae gravidarum are also at higher risk (9). Most striae fade and shrink postpartum, however they rarely disappear. There is no specific evidence based treatment, however numerous creams, emollients, and oils are commonly used throughout pregnancy.

Hyperpigmentation is another extremely common dermatological condition seen in almost all women (90%) during pregnancy, especially during the first trimester of pregnancy. The areas which are most commonly affected tend to be the areolae, axillae, and genitals, however scars and naevi may also be darkened. The linea nigra is a line that often forms when the abdominal linea albens darkens during pregnancy. This pigment fades after pregnancy, however like striae, they rarely disappear completely (10).

Melasma develops in up to 70% of pregnant women, especially those with dark complexions (8). This condition usually presents as irregular areas of pigmentation with a sharp border in a symmetrical pattern, seen on the forehead and temples, or on the central face. This condition may be cosmetically displeasing, however melasma usually fades completely after pregnancy which is very reassuring for mothers. Sunlight exposure worsens melasma, therefore strict sun protection may prevent the condition from developing or worsening. In some cases, melasma may recur with future pregnancies or with oral contraceptive use (11).

Hair changes are common during pregnancy, with either an increase or decrease of growth and production of hair (8). Various women develop hirsutism (hair growth in a male pattern) on the face, limbs, and back due to endocrine changes during pregnancy. Hirsutism is particularly seen in women with dark hair, and usually resolves postpartum. Women may also notice thickening of scalp hair during pregnancy, followed by a compensatory increased shedding of hair postpartum, called telogen effluvium.

Nail changes also commonly occur during pregnancy, namely increased brittleness, transverse grooves, onycholysis, and subungual keratosis (10). Such conditions generally resolve postpartum.

Vascular changes in pregnancy are attributed with the elevated oestrogen levels which in turn cause an elevated vascularity and increased blood volume. Spider telangiectases are very common in pregnancy, and appear in areas drained by the superior vena cava, namely the face, neck, upper chest, and arms. Palmar erythema and non-pitting oedema of the legs due to increased hydrostatic pressures are also seen in up to half of normal pregnancies. Varicose veins of the legs, haemorrhoids, vulvar varicosities, and pyogenic granulomas can also appear as complications of pregnancy. Most of these vascular changes resolve postpartum, however observation is always important to monitor progression and

potential bleeding (12).

(2) Pre-existing skin conditions

During pregnancy there is a shift in the immune system from T helper 1 to T helper 2 lymphocyte cells, thus switching from cell-mediated to humoral immunity. This is an important immunological change to ensure that the mother's body doesn't reject the developing foetus. However this in turn influences women's susceptibility to skin disease, as it causes an increase in likelihood of autoimmune diseases and a decreased cell mediated immunity (13).

Pre-existing skin conditions may therefore change during pregnancy. Generalised pustular psoriasis, melasma, periorificial dermatitis, rosacea, skin tags, systemic lupus erythematosus, and vesicular hand dermatitis generally worsen during pregnancy. Atopic dermatitis and psoriasis may worsen, improve or stay the same.

(3) Pregnancy specific skin conditions

There are also skin conditions that occur specifically during pregnancy. These are called pregnancy-specific dermatoses, and most commonly include pruritic urticarial papules and plaques of pregnancy (PUPPP), prurigo of pregnancy, intrahepatic cholestasis of pregnancy, and pemphigoid gestationis (10).

PUPPP is the most common pregnancy specific dermatosis, and presents as an intense pruritic rash generally on the abdomen along the striae. This disorder is more common with first pregnancies and multiple gestations. There is no specific treatment for PUPPP, and there are no associated negative consequences on one's pregnancy, however antihistamines and topical steroids may be used to symptomatically treat the pruritus associated with the PUPPP rash (8). This typically resolves one to two weeks after delivery.

Prurigo of pregnancy, characterised by extremely itchy papules or nodules, is also occasionally seen during pregnancy, and may persist for weeks to months postpartum (14). There is no clear cause, or adverse effects of this condition on the mother or foetus. Mild-potency topical steroids and oral antihistamines may provide symptomatic relief.

Intrahepatic cholestasis of pregnancy classically presents as severe pruritus throughout the third trimester. Diagnosis of this condition is based on both clinical history and presentation: pruritus with or without jaundice, no primary skin lesions, and laboratory markers of cholestasis (elevated serum bile acid levels and alkaline phosphatase levels with or without elevated bilirubin levels) (15). Intrahepatic cholestasis of pregnancy usually resolves postpartum. Oral antihistamines may provide symptomatic relief of pruritus.

Pemphigoid gestationis (also referred to as herpes gestationis) is a rare autoimmune blistering skin disorder, which generally improves in late pregnancy, with postpartum exacerbations (16). Patients with a history of pemphigoid gestationis tend to have an increased risk of other autoimmune diseases. Antenatal surveillance is important, as this disorder may cause lesions in newborns or mild placental failure. Oral antihistamines and systemic topical corticosteroids may be used for patients with mild pemphigoid gestationis, and oral corticosteroids may be used in more severe cases (10).

CONCLUSION

Psychiatric conditions during pregnancy are not as rare as one might think. Depression and anxiety disorders are some of the common psychiatric manifestations that may occur throughout pregnancy. It is therefore crucial to raise awareness about such conditions, as proper screening, early identification and treatment of such disorders can prevent the various potential short and long term consequences on the mother and baby. Both psychotherapy and pharmacotherapy should be considered, with the benefits and risks always being compared.

Dermatological conditions are also commonly seen during pregnancy. Hormonal changes may cause benign skin conditions such as striae gravidarum; hyperpigmentation; and hair, nail, and vascular changes. Pre-existing skin conditions may be exacerbated such as generalised pustular psoriasis, melasma, periorificial dermatitis, rosacea, skin tags, systemic lupus erythematosus, and vesicular hand dermatitis. Finally, some women may experience pregnancy specific dermatoses, most commonly PUPPP, prurigo of pregnancy, intrahepatic cholestasis of pregnancy, and pemphigoid gestationis. Such skin conditions can cause temporary or permanent negative effects, so early diagnosis is important to minimise any risk on both the mother and foetus, and treat any complications which may arise.

Education during pregnancy remains one of the most important aspects, and regular compliance with antenatal care is imperative to ensure the safety and wellbeing of both the pregnant mother and foetus.

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The Effects of Smoking on Pregnancy and Breastfeeding

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According to the latest Maltese National Obstetric Information System (NOIS) Annual Report of 2020, 8% of expecting mothers were reported to smoke throughout their pregnancy (1). Cigarette smoking during pregnancy as well as lactation is associated with detrimental outcomes for both the mother and baby. However, cigarette smoking is one of the most crucial preventable causes for such outcomes (2). Apart from active smoking by the expecting mother, passive smoking (or second-hand smoking) is also harmful to the baby as it is comprised of the same tobacco smoke toxins found in active cigarette smoking. Furthermore, it has been found that third-hand smoke exposure, which occurs when tobacco components precipitate on surfaces and adhere to dust particles, increases exposure to nicotine especially indoors (3).

CIGARETTE SMOKING AND THE BODY

Tobacco smoke is a complex mixture consisting of more than 4,000 harmful chemicals (4). Some of the components include carbon monoxide, nicotine and carcinogens such as aromatic amines, polycyclic aromatic hydrocarbons and tobacco-specific N-nitrosamines, which have all been associated with adverse effects on foetal life (4). The smaller particles of nicotine are able to infiltrate deeply into the lung tissue, eventually crossing the lung barrier and entering into the blood circulation. Therefore, apart from causing localised injury to the lungs, smoking can also alter the innate and adaptive immunity and consequently increase C-reactive protein, fibrinogen, interleukin-6 levels and white blood cell counts respectively (5,6). Moreover, nicotine has been proven to cross the placenta as high amounts of cotinine, which is a nicotine metabolite, have been seen in the amniotic fluid of pregnant smokers (7,8).

SMOKING AND THE UNBORN BABY

The detrimental effects of maternal smoking during pregnancy may be observed from the first trimester. The basement membrane thickens and consequently increases the changes in placental tissue and morphology (9). This would also lead to a decrease in vascularisation and therefore, less nutrients and oxygen delivery to the foetus (10).

Maternal smoking has also been strongly linked to preterm birth (<32-week gestational age) (11). A dose-response relationship has been observed between the numbers of cigarettes smoked and pregnancy duration (12). A strong association between maternal smoking and birth complications such as premature membrane rupture, has also been reported (13). Preterm babies have been documented

to suffer from long-term decreased lung function values (14,15) throughout their lives and also increased hyper-responsiveness of the airway. Prematurity (16) and corticosteroid exposure (17) to help lung maturation after premature birth is directly linked to asthma.

Smoking during pregnancy is linked to foetal growth restriction and with a decrease in birth weight of around 150-200g (18,19). Maternal smoking during pregnancy is associated with reduced head size and femur length (20). Furthermore, the foetal skeletal growth is also affected as maternal smoking decreases the buildup of foetal bone mass. This occurs due to diminished calcium absorption in the intestines, and oxygen supply and nutrients to the growing foetus (21,22). The influence of maternal smoking has been shown to have a long-lasting effect on the skeletal development of the offspring. This could be due to the intrauterine processing of the growth hormone/insulin-like growth factor-1 axis (23,24). Therefore, smoking during pregnancy could expose the offspring to an increased lifetime risk of defective bone health such as osteoporosis.

One of the adverse effects of maternal smoking is the increased possibility of intrauterine growth retardation (IUGR) (25) and consequently also linked to poor lung function (26). Maternal smoking also increases the risk of morbidity following viral respiratory illnesses (27). Exposure to tobacco increases the chances of respiratory infections and wheezing illnesses (28)

EFFECTS ON BREASTFEEDING

The World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF) both recommend that infants start breastfeeding within the first hour of birth and are solely breastfed for the first 6 months of life (29). Breast milk contains the most important macronutrients (vitamins, proteins, lipids and carbohydrates) needed for the proper development of the newborn. It also contains vital bioactive substances such as antimicrobials, hormones and growth factors, amongst others, that are crucial at this stage.

Cigarette smoking affects the breastfeeding stage of pregnancy as it decreases the levels of prolactin and consequently reduces the milk supply (30,31). It also changes the milk composition and taste. When a woman is breastfeeding, the levels of the hormone somatostatin are decreased. However, in smoking mothers the somatostatin levels are increased which leads to decreased milk production (32). When breast milk is given to the baby, nicotine is taken up by the digestive system and the baby's liver metabolises the nicotine to cotinine (33). These substances in the baby's circulation can lead to increased baseline heart rate (34). Newborn infants of smoking mothers show delayed sucking reflex and decreased sucking pressure whilst breastfeeding. Such differences in breast emptying and stimulation would alter the endocrine hormones which further contribute to decreased milk production in smoking mothers (35).

CHANGE IN BREASTMILK FLAVOUR AND COMPOSITION

Nicotine in breast milk has been reported to diminish the baby's appetite and desire for breastfeeding milk. The total fat concentration in the breast milk of smoking mothers is found to be lower by approximately 19% to 26% (36,37). In normal lactation, the hormone prolactin augments the enzyme activity of lipoprotein lipase which speeds up the production of free fatty acids to the mammary gland (38). In smoking, however, the action of lipoprotein lipase on the liver is inhibited and therefore lipolysis is diminished and triglycerides, low-density lipoproteins and cholesterol levels are increased in maternal blood (36,39). Furthermore, decreased amounts of long chain polyunsaturated fatty acids, such as omega-3 fatty acids, have been observed in women who smoke.

Smoking also increases the levels of certain heavy metals in breast milk (40). The most dangerous is cadmium, which is a toxic metal and which diminishes the metabolism of certain microelements such as iron, magnesium, copper, zinc and selenium (41–43). These microelements are vital for the normal development of the foetus and infant. Moreover, in mothers who smoke even during lactation, iodine levels have been found to decrease in breast milk. Iodine is essential in the development of thyroid hormones and reduced iodine is linked to diminished motor function, poorer cognition and brain damage (44).

Cytokines are important in regulating normal cellular regulation and growth. They bind to specific receptors which are found on immune system cells and play a role in the inflammatory process. In the initial term of lactation, the colostrum and transitional milk have increased levels of specific cytokines such as tumour necrosis factor (TNF) α, TNF β, interleukin (IL)-1β, IL-2, IL-4 and IL-5 amongst others. These cytokines are vital for organogenesis in early development as the neonates' organs are still not fully developed (45,46). TNF α which plays a crucial role against infection and trauma, was found to be significantly lower in smoking mothers' breast milk. Furthermore, decreased concentrations of IL-1β and IL-8 in colostrum, and IL-6 in mature milk were observed in lactating smoking women (47).

It has been observed that women who smoke heavily during pregnancy and breastfeeding have an increased rate of their offspring developing early stage leukemia (48). Also, women who breastfeed and smoke run a 50% increased risk of colic in babies (49).

The presence of nicotine in the body promotes the formation of oxygen radicals and concurrently decreases the antioxidant function of the lungs, which contributes to DNA mutations (50,51). This mechanism prevents the correct development of the lungs and leads to structural changes (52–54).

Maternal smoking has been identified as a significant risk factor to sudden infant death syndrome (SIDS) (55) and has also been linked to an increased risk for respiratory infections and allergies in

children. As the child grows older, the adverse effects of maternal smoking may still be felt as the infant has a higher probability of developing upper and lower respiratory tract infections and otitis media (56). A high nicotine level in breast milk has also been linked to a decrease in the child's active sleeping time as compared to those mothers who avoid smoking prior to breastfeeding (53.4 minutes versus 84.5 minutes) (57)

SMOKING CESSATION

Smoking cessation advice in preconception and antenatal care needs to be further reinforced because it has been shown that smoking reduction can lower the risk of impaired foetal growth (18). Cigarettes continue to be the most common used tobacco product even during pregnancy, nonetheless, other forms of tobacco such as vaping, cigars and e-cigarettes are gaining popularity (58). However, data regarding the effects on the maternal population is still very limited. A wrong perception exists that vaping is a safer alternative to cigarette smoking since the smoker is not inhaling the products of tobacco combustion, however, these products still contain nicotine or its salts (59,60)

The National Institute for Health and Care Excellence (NICE) recommends that healthcare practitioners offer cognitive behaviour therapy, motivational interviewing and structured selfhelp and support from professional services for smoking cessation. Nicotine replacement therapy (NRT) risks and benefits should be discussed at length with pregnant women who smoke, especially with those who do not wish to use non-pharmacological therapy. NRT should only be prescribed once the pregnant woman stops smoking and should be started two weeks after smoking has stopped. It is important to advise pregnant women that nicotine patches shoud be removed prior to going to bed. Also, bupropion and varenicline should not be promoted to pregnant or breastfeeding women (61).

CONCLUSION

In conclusion, healthcare professionals should support both expecting parents to quit smoking in a holistic manner in order to ensure that the baby's health is safeguarded. The expecting mother should be encouraged to reduce the number of cigarettes smoked in order to decrease the dose-response relationship. A smoke-free environment needs to be adopted by the whole family in order to ensure the least exposure possible to tobacco.

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The Impact of Chlamydia and Gonorrhoea Infections on Fertility, Pregnancy and the Newborn

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INTRODUCTION

The Centres for Disease Control and Prevention (1) states that the term “sexually transmitted infection” (STI) refers to an infectious pathogen transmitted sexually, and “sexually transmitted disease” (STD) refers to a disease which has developed from the infection (1). The two most common STIs which are reported in the European Union and which impact fertility are chlamydia and gonorrhoea. In fact, around 250 000 new cases of chlamydia infection and 100 673 new cases of gonorrhoea infection are reported each year in Europe (2). Chlamydia is a sexually transmitted infection caused by the Chlamydia trachomatis bacterium. Gonorrhoea, informally known as the clap (‘pixxikalda’ in Maltese), is also as STI caused by the bacterium Neisseria gonorrhoeae (3). Being the two most common STIs reported, the effect of chlamydia and gonorrhoea infection in women, before and during pregnancy and in the baby, will be discussed.

POTENTIAL HARM OF CHLAMYDIA AND GONORRHOEA INFECTION TO WOMEN

Most females who become infected with chlamydial and gonorrhoea infection of the cervix are asymptomatic (1). Yet asymptomatic infections do not mean that there is no harm caused. Asymptomatic infections in fact are more likely to develop into pelvic inflammatory disease (PID). PID refers to uterus, fallopian tubes and/or ovary infection. PID may cause infertility since it predisposes to the risk of the reproductive organs to become scarred. The scarring of the reproductive organs may also increase the risk of chronic pelvic pain, abnormal vaginal bleeding, fever, dysuria, increased urinary frequency and ectopic pregnancy (4). Both chlamydia and gonorrhoea infection increase the risk of fallopian tube scarring. If left untreated, chlamydia develops in PID in about 10-15% of women (1). It is interesting to note that pregnant women do actually have some degree of protection against possible problems caused by STI infections (4). It is also important to note that infected women treated for gonorrhoea and/or chlamydia after 3 or more days of symptoms had significantly more infertility than those treated earlier (5).

POTENTIAL HARM OF CHLAMYDIA AND GONORRHOEA INFECTION TO THE BABY

More than half of the babies born to mothers infected with chlamydia will become infected themselves (6). Chlamydia may harm the baby by resulting in spontaneous miscarriage, preterm birth, premature rupture of membranes, conjunctivitis and pneumonia. Pneumonia has an onset of mainly 1-3 months of age. Conjunctivitis increases the risk of blindness in the baby (1). Conjunctivitis due to chlamydia typically occurs one week after birth while in gonorrhoea it typically occurs 2–5 days after birth (3).

Eye infections including conjunctivitis in a newborn are rarely caused by gonorrhoea. If this does happen, though, it can result in permanent blindness due to a condition referred to as gonococcal ophthalmia neonatorum. Fortunately, blindness caused by gonorrhoea can be prevented by administration of prophylactic antibiotics (1). Gonorrhoea may also cause low birth weight, premature birth, miscarriages, scalp infections, upper respiratory infections, urethritis, or vaginitis in the newborn. The infection can also enter the bloodstream causing generalized illness and may also spread throughout the body including joints causing arthritis, or inflammation of the tissues in the brain or spinal cord (2 & 3).

TRANSMISSION OF INFECTION

Both chlamydia and gonorrhoea can be transmitted during vaginal sex, anal sex, oral sex and/or direct contact with infected tissue. Chlamydia and gonorrhoea are both also vertically transmitted infections meaning that the infection can be transmitted via mother-to-baby transmission during pregnancy and/or childbirth (mainly vaginal childbirth) (1 & 7). According to Manoj et al (6) the risk of one becoming infected from an infectious host depends on the number of bacteria one is exposed to.

TREATMENT OF THE PREGNANT MOTHER

Chlamydia infection can be effectively cured with antibiotics. Guidelines recommend that during pregnancy uncomplicated chlamydia can be treated with azithromycin and amoxicillin. In fact, these antibiotics have cure rates of 95% for uncomplicated chlamydia. Clinical studies have shown that azithromycin is safe and effective to use in pregnancy. Because of concerns of chlamydial persistence after exposure to penicillin, amoxicillin can be administered as an alternative therapy for pregnant women. Following treatment, the pregnant mother should be tested again after three months to check for reinfection (1). Sexual partners should also be tested and treated prophylactically (8).

Pregnant women infected with gonorrhoeae should be treated with ceftriaxone, together treatment for chlamydia if infection has not been excluded (8). CDC (1) currently recommends that infected patients with gonorrhoea should avoid sexual contact with others until at least one week past the final day of treatment in order to prevent spreading infection.

TREATMENT OF THE INFECTED BABY

Erythromycin base or ethylsuccinate is the treatment of choice for infected newborns. Oral erythromycin remains the recommended treatment for neonatal conjunctivitis and pneumonia caused by chlamydia (CDC, 2021). Prophylactic treatment of the newborn is not recommended because the efficacy of prophylaxis is still not known (8).

Newborns born from an infected mother or who is at high risk of gonorrhoea infection should be tested for gonorrhoea at exposed sites, mainly the conjunctiva, vagina, rectum, and oropharynx) and treated prophylactically for gonorrhoea (1). For newborns, erythromycin ointment is recommended as a preventative measure for gonococcal infant conjunctivitis. Erythromycin ophthalmic ointment should be administered into both eyes as soon as possible after delivery, regardless of whether the baby has been delivered via a normal vaginal birth or via caesarean section (8). If erythromycin ointment is unavailable, babies at risk for gonorrhoeae infections can be administered ceftriaxone (1). In cases of disseminated gonococcal infection and gonococcal scalp abscesses among newborns one should take blood cultures, lumbar pucture or joint aspirate. Antimicrobial susceptibility testing should then be performed. Ceftriaxone or cefoxtamine should be administered. When administering ceftriaxone caution should be taken in particular to newborns with hyperbilirubinemia, especially those born prematurely (7 & 1).

SCREENING FOR CHLAMYDIA AND GONORRHEA IN PREGNANT FEMALES

It is important to note that pregnant women are at increased risk for chlamydia and gonorrhoea (1). It is reported that women are twice as likely as men to acquire gonorrhoea or chlamydia during a single act of unprotected intercourse with an infected partner (5). Yet whom should be screened for these STIs?

- Bigger risk of STIs is present in pregnant females particularly women who either have a: new sex partner, more than one sex partner, a sex partner who has an STI, having sex for money and drugs, and/or a sex partner who has concurrent partners. Therefore, these patients should be screened routinely for Chlamydia trachomatis and Neisseria gonorrhoeae at their first prenatal visit.

- Pregnant females in their third trimester should be retested (even if at prenatal visit they have tested negative) but they are still at increased risk for these STIs infections (1).

There is evidence that antenatal chlamydial screening and treatment interventions may lead to decreased adverse pregnancy and infant outcomes, such as premature rupture of membranes, preterm birth and low birthweight (9).

CONCLUSION

The best hope for reducing the incidence of infertility and complications in the pregnant mother and her baby depends on prevention, early detection and treatment of both asymptomatic and/or symptomatic infections. The importance of protecting future fertility by avoiding high-risk sexual activities and the compulsory use of condoms must be stressed. Concurrently, there must be increased awareness by health care providers for screening and early effective treatment if positive to prevent complications (3).

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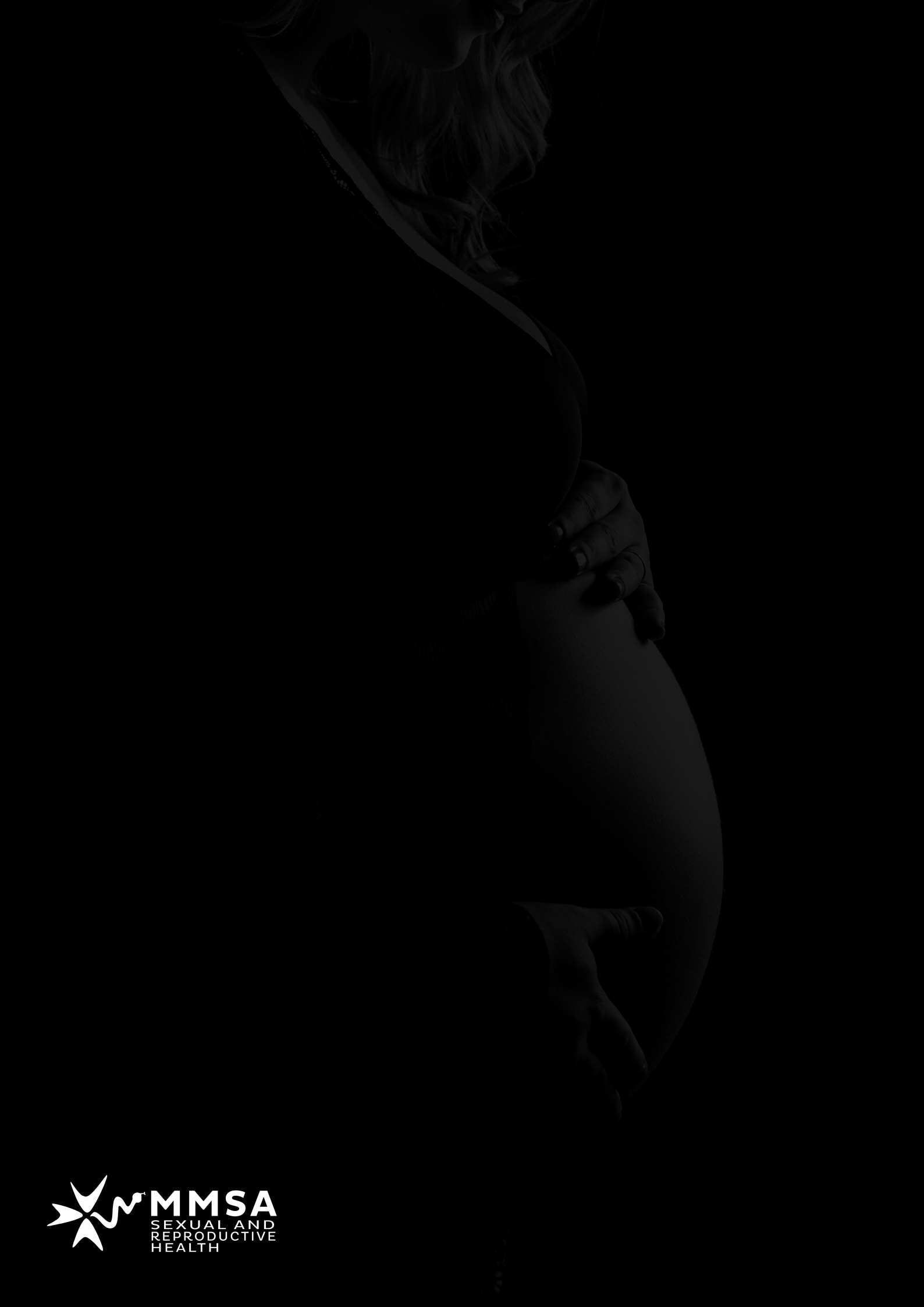

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