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REVIEW

Management of brain tumours in pregnancy

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Abstract

Key message

Pregnant women diagnosed with brain tumours face unique challenges due to the physiological and hormonal changes of pregnancy, which can exacerbate tumour growth and symptoms. A multidisciplinary approach involving neurosurgeons, obstetricians, and other specialists is essential for optimising maternal and foetal outcomes.

- **Diagnosis:** Symptoms such as headache, nausea, vomiting, and seizures may overlap with typical pregnancy discomforts, making detailed neurological and imaging assessments crucial.
- **Management:** Treatment strategies are individualised based on the tumour type, size, location, and pregnancy stage. Options include:
    - Conservative management with regular monitoring.
    - Surgical intervention, preferably in the second trimester, for cases with severe symptoms or rapid tumour growth.
    - Steroid therapy to manage tumour-induced oedema and support foetal lung maturation in cases of preterm delivery.
    - Antiepileptic medications and other symptom-specific therapies are used when necessary, though care is taken to minimise foetal exposure to teratogenic drugs.
- **Timing of Delivery:** Caesarean section is often preferred to avoid the risk of increased intracranial pressure during vaginal delivery. In cases requiring surgery near term, simultaneous caesarean delivery and neurosurgery may be considered.
- **Postpartum Care:** Post-surgical and post-treatment monitoring is critical, especially for potential complications like pituitary suppression or the need for further cancer therapy. Fertility preservation techniques and counselling should be considered for women undergoing chemotherapy or radiotherapy before pregnancy.
- **Prognosis:** Outcomes depend on tumour type, timing of diagnosis, and prompt management. Preconceptual optimisation for women with a history of brain tumours may improve obstetric outcomes and reduce the risks associated with tumour progression during pregnancy.

INTRODUCTION

Brain tumours are a challenging condition that pose a serious risk to life. Challenges are increased during pregnancy and could worsen the outcomes of pregnancy. The known complications are foetal growth restriction, preterm birth, increased emergency caesarean section, and increased maternal mortality.[1,2] Since only a few cases of brain tumours have been reported during pregnancy, there is a dearth of knowledge, particularly on management. Consequently, neurosurgeons and obstetricians find it a challenging condition, and greater understanding is required in the diagnosis and management of malignant brain tumours during pregnancy.[3] Thus, this article highlights the epidemiology, tumour types, aetiology, clinical features, management, and prognosis of brain tumours in pregnancy.

Epidemiology

In general, brain cancer is uncommon compared to other types of malignancies. According to the National Cancer Institute, USA, the annual rate of new brain and other nervous system cancer cases was 6.2 per 100,000 men and women. The annual death rate was 4.4 per 100,000 men and women. Based on data of diagnoses and deaths from 2016 to 2020, brain tumours are the sixth most prevalent cause of cancer-related death.[4]

Several research studies have been conducted to find an association between brain tumours and pregnancy. The first report of such an association was described by Simon in 1989, who found that about 90 women in the United States have had brain tumours during pregnancy each year, based on probability calculations.[1] About 31,988 central nervous system (CNS) tumours affect women of reproductive age (20-44 years). The risk of developing a brain tumour in pregnant and non-pregnant women is believed to be 1 in 1000-2000.[3] The incidence of primary malignant brain tumours was reported to be lower in pregnant mothers compared to non-pregnant women.[1,2] However, the relative prevalence of each type of brain tumour appears to be thesame in both groups.[1,2,5]

Tumour types

None of the brain tumours seem to occur more frequently during pregnancy.[2,5] Though some types of brain tumours express progesterone receptors that can bind with the high levels of progesterone produced during pregnancy, the production of angiogenic factors like placental growth factors, hormonal and physiological changes during pregnancy together may enhance tumour growth and worsen pregnancy outcomes.[6]

Malignant gliomas and benign meningiomas are the two most common types.[3] Glial cell-derived tumours called gliomas appear more frequently in the first two trimesters of pregnancy. Arachnoid cap cells in the meninges covering the brain are the source of meningiomas, manifesting more frequently in the third trimester.[1,2] Meningiomas are known to express a high level of progesterone receptors, and a high level of progesterone expression in the third trimester might be the reason for the exacerbation of symptoms during this period. Hence, pregnancy appears to aggravate both gliomas and meningiomas.[1,6]

Pituitary tumours are also not uncommonly seen in pregnant women. Five to fifteen percent of women with pituitary tumours may experience tumour expansion during pregnancy due to the pituitary gland's growth due to oestrogen-stimulated hyperplasia and hypertrophy of prolactin-producing lactotrophs. The pituitary gland's physiologic expansion might enhance the tumour's growth to aggravate symptoms in women. Tumour growth may also accelerate during breastfeeding. Following pregnancy and lactation, most pituitary tumours regress with cessation of symptoms.[7] An elevated prolactin level in pregnancy does not always indicate the presence of a prolactinoma since pregnancy per se increases the blood prolactin level. Cushing syndrome with an adrenocorticotropic hormone-producing tumour and growth hormone-producing tumours are less frequently seen pituitary tumours in pregnancy.[7]

Acoustic neuroma, often now referred to as vestibular schwannoma, is a benign tumour that develops from the vestibular branch of the vestibulocochlear nerve, and colloid cysts in the anterior third ventricle have also been observed in pregnant women.[1] Although uncommon in pregnant women, metastasised brain tumours from other primary sites, such as breast or lung, have also been reported. However, gestational trophoblastic disease following ectopic pregnancy, term pregnancy, molar pregnancy and miscarriage might cause brain metastasis. In the context of pregnancy, other rare tumour types have also been documented in the literature, such as craniopharyngiomas, ependymomas, haemangioblastomas, pineal region tumours, medulloblastomas, primary central nervous system lymphomas, paragangliomas, primary meningeal sarcomas, and dysembryoplastic neuroepithelial tumours.[1]

Aetiology

Damage or alteration to genetic material is involved in the potential pathogenesis of tumours. This damage may affect a gene that is responsible for controlling one of the following mechanisms: the pace of cell division, repairing deoxyribonucleic acid (DNA) damage, apoptosis (if the damage is too much to be repaired), and controlling the rate of further

proliferation of the damaged DNA . The damage may be attributed to either congenital or environmental factors or both.[8] Though the exact cause of a brain tumour is unknown, gender, age, some immunological disorders, chemical and radiation exposure, and genetic ties are the known risk factors for brain tumours.[9]

Occupational chemical exposure is more common in women working in the pharmaceutical, rubber, and oil refining industries, and they might have a greater prevalence of specific types of brain tumours. Moreover, the risk of getting a brain tumour may increase with radiation therapy exposure, mainly when it occurs early in life.[9] Family history also may influence the aetiology of brain tumours, and it is best seen with families having a history of uncommon brain tumours that have been shown to carry genetic disorders such as Li-Fraumeni syndrome, Neurofibromatosis (NF1 and NF2) and Von Hippel-Lindau disease.[2,9]

It has been demonstrated that hormonal contraceptives or hormone replacement treatment increase the likelihood of brain tumour-related symptoms. Additionally, some specific menstrual cycle phases (luteal) and pregnancy are linked to worsened symptoms.[7] When compared to nulliparous patients, it has been shown that multiparous women had a lower risk of acquiring gliomas and meningiomas. It does not, however, correlate with the finding that pregnancy promotes tumour growth. Additionally, it has been suggested that menopause raises the risk of meningioma. High parity, advanced age at first delivery, and time since last delivery were not strongly associated with an increased risk of developing brain tumours during pregnancy.[10]

DIAGNOSIS

Clinical features

Patients with brain tumours present with vague symptoms like headache, nausea, or vomiting and focal neurologic deficits such as visual changes and hemiparesis. One of the reasons for these symptoms is increased intracranial pressure caused by the mass of the tumour. The hypervolaemic status of pregnancy may worsen preexisting intracranial pressure due to a physiological increase in intravascular volume and water retention.[11]

Headache is one of the common symptoms of brain tumours with and may have varying characteristics and intensities. Increased intracranial pressure-related headaches start gradually and get worse over time. It is characterised by daily headaches, getting worse in the morning or after actions that raise intracranial pressure, such as lying down, coughing, exerting oneself, or bearing down.[1]

Nausea and vomiting are general symptoms of brain tumours and raised intracranial pressure. These symptoms are common in pregnancy, such as ordinary morning sickness or the more severe illness known as hyperemesis gravidarum. Pregnant women mostly experience nausea and vomiting in the first trimester; however, it can persist and get worse in the second and third trimesters in women with brain tumours. Moreover, pregnant mothers with intracranial tumours have been reported to have behavioural changes, memory loss and urinary incontinence.[12]

Pregnant women with pituitary tumours have new vision field and endocrine abnormalities, and these symptoms usually occur between the 10th and 20th week of pregnancy. The optic chiasm is compressed by the tumour, which can be either brought on by the rapid growth of the tumour or by the normal physiological expansion of the pituitary gland during pregnancy.[7] Rarely, postpartum blindness also has been reported with undiagnosed brain tumours.[12]

Seizures are a frequent and sometimes fatal complication of primary or metastatic brain tumours, and they are related to the mass effect of brain tumours. A comprehensive assessment is required to diagnose the brain tumour since seizures can also be linked to different causes, such as metabolic alterations and poisoning in the first trimester.[13]

Eclampsia, resulting from pregnancy-related hypertension or an intracranial tumour, can cause seizures. However, clinical, biochemical, and imaging assessments will aid in determining differential diagnoses during pregnancy.[14] Patients with vestibular schwannomas frequently experience imbalance, tinnitus, and hearing loss.[1] Additionally, brain tumours rarely present as hemiparesis and are commonly reported in the 2nd and 3rd trimester.[12]

The examination might facilitate the brain tumour diagnosis along with the history. Detailed neurological and ophthalmologic examinations are essential in diagnosing a brain tumour in pregnancy.[2] A new onset of seizures during the second half of pregnancy more likely represents eclampsia than a brain tumour. In contrast to focal seizures, which are most often associated with brain tumours, seizures identified with eclampsia are usually generalized in nature and are accompanied by hypertension, proteinuria, hyperreflexia, and the remainder of the hallmark clinical features of this disease.[15] Localised tumour invasion or compression of adjacent brain tissue eventually leads to focal neurologic findings determined by the tumour location. For instance, if located in the dominant hemisphere, frontal lobe lesions may cause cognitive slowing, contralateral hemiparesis, or even expressive aphasia (inability to produce speech). The extent to which a tumour in a particular brain location causes neurologic deficits is based largely on the degree of its mass effect.[15]

INVESTIGATIONS

Since most of the common clinical features of brain tumours are mimicked by usual pregnancy symptoms, appropriate investigations play a vital role in diagnosis. Apart from the basic blood investigations, hormone profiles and imaging studies facilitate brain tumour diagnosis. Serum pituitary hormone levels such as prolactin, thyroxine and corticosteroid levels can offer crucial information, particularly in pituitary tumours. It will not only aid in the diagnosis but also help to screen and monitor the response to treatment.[2]

Imaging studies are recommended in pregnant women with high suspicion in the clinical assessment. Computed tomography (CT) and magnetic resonance imaging (MRI) are the basic diagnostic imaging methods that provide adequate information about the brain tumour and its distant spread.[16] MRI is superior in image quality, with increased sensitivity of diagnosis and lack of radiation compared to CT.[16] CT imaging is helpful for the initial diagnosis of a brain tumour, and it offers definite advantages over MRI, such as effectiveness and greater accessibility. Multiple studies have shown that cranial CT scanning is safe for the foetus, especially with abdominal lead shielding techniques.[1]

The diagnostic value of cranial imaging is improved by administration of intravenous (IV) contrast. All individuals, including pregnant women, could have nephrotoxicity and allergy-related adverse effects from the contrast medium used in CT scanning. However, it has not been proven to cause congenital abnormalities in foetuses. Foetal hypothyroidism is one of the less proven complications in a newborn delivered by a pregnant mother undergoing contrast CT during her pregnancy. Therefore, thyroid function is assessed during the first week of the newborn. Studies have shown that Gadolinium-based contrast is less likely to cause adverse effects than CT contrast medium. It might have minimal nephrotoxicity and is less likely to cause an allergic reaction. The contrast crosses the placenta and is excreted by the foetus' kidneys into the amniotic fluid; no congenital abnormalities have been found in the foetus.[16]

MANAGEMENT

Management of brain tumours in pregnancy is individualised depending on the type, location, symptoms, and time of tumour diagnosis during the pregnancy (Figure 1).[17] In pregnancy, management should be planned to balance the risks against the benefits. It can be managed conservatively, medically, or surgically to control the symptoms until delivery with intense monitoring, to identify the best time when definitive treatment can be administered.[17] On the other hand, the pregnancy might have to be terminated if it could endanger the pregnant mother's life. With the inputs from the multidisciplinary team, treatment must commence as early as possible, which is legal in Sri Lanka.[5,13]

For brain tumours diagnosed in the first or second trimester, surgery is safer to perform in the second trimester while continuing with the pregnancy. This is due to the vulnerability of the foetus during the first trimester and the higher risk of intraoperative bleeding during the third trimester. If tumour growth and symptoms are not severe, pregnancy can continue until reasonable foetal maturity and may be delivered by cesarean section or induction of labour at 34 to 36 weeks. Routine laboratory tests and imaging can be performed for monitoring purposes.[18] If the disease progresses more during pregnancy, priority is always given to the pregnant women, and treatment may begin immediately while terminating the pregnancy before the viable period of the foetus.[13] Caesarian births are often preferred since vaginal deliveries increase intracranial pressure.[6] Therefore, the balance between foetal maturation and tumour progression and maternal outcome should be considered when managing brain tumours in pregnancy.[19]

Steroid therapy plays a significant role in managing brain tumours in pregnancy. Steroids reduce vasogenic oedema around the tumour and give symptomatic support to pregnant women.[12] On the other hand, steroids increase surfactant production in the foetal lung and improve respiratory distress, especially in preterm deliveries.[2,6] Steroids are given to facilitate foetal lung maturation and to prevent intracranial haemorrhage in the infant when preterm birth is expected within 24-34 weeks of gestation.[6] Despite these advantages, prolonged steroid treatment has a small but possible risk of causing an adrenal insufficiency in the newborn. Suppressing the foetal pituitary axis, which causes newborn hypoadrenalism, is a serious issue with the maternal treatment of glucocorticoids during pregnancy. However, this condition is an uncommon side effect of glucocorticoid therapy intrauterine administration.[2] Mannitol should be taken with caution during pregnancy as it may impair the circulation of the foetus and may lead to foetal dehydration.[2,13]

Antiepileptic medications (AEDs) are used to treat individuals with brain tumours, although they are controversial when administered during pregnancy. Several AEDs have teratogenic effects, which can cross the placenta.[13] Antiepileptic medications during the first trimester could increase the chance of serious congenital abnormalities.[13] However, it is generally agreed that the danger of recurrent seizures surpasses any potential adverse effects of the medicine, including any potential teratogenicity. Hence, the authors recommend the utilisation of AEDs only when a pregnant mother experiences recorded seizures and should not be given for a single seizure or seizure prevention.[13]

Chemotherapy is often postponed until the delivery to avoid the risk of congenital malformations, carcinogenesis, organ toxicity, growth retardation to the foetus, and miscarriage, especially when administrated in the first trimester.[16] However, several drugs used to treat pituitary tumours appear to be safe to use during pregnancy and may postpone or prevent the need for surgical removal of the tumour. Bromocriptine and dopamine analogues have been reported to have good safety profiles in prolactin-secreting pituitary tumours, although they should be taken cautiously in pregnant and breastfeeding women.[20] Additionally, octreotide is used to treat acromegaly, slowdown the growth of tumours, and appears safe in pregnant women.[21] Common systemic glioma therapies like temozolomide and bevacizumab (vascular endothelial growth factor receptor inhibitors) are often avoided during pregnancy.[21]

Radiation therapy (RT) is not recommended until delivery due to the deleterious effects that could occur in the foetus. Radiation administered during the first trimester has the potential to result in congenital abnormalities, childhood cancer, leukaemia and mental retardation.[22] However, if RT is administered in the second or third trimester, the hazard to the baby could be reduced, but it is highly recommended to avoid it. Strategies to minimise the radiation affecting the foetus and prevent unfavourable side effects are described, including limiting the dosage, employing abdominal lead shielding, and adjusting the patient's posture throughout the therapy.[22] A safer way to provide focused radiation therapy is through stereotactic radiosurgery, which uses tools like the Gamma Knife or CyberKnife as they minimize the exposure of the foetus to radiation.[19] Long-term exposure to chemotherapy and radiation therapy during pregnancy has been demonstrated in studies to have no negative impact on overall health and neurocognitive development in children. However, a few cases were reported with spastic diplegia and mild psychomotor impairment.[19]

Surgery is a common management option, especially when the tumour is large with aggressive symptoms during pregnancy. The caesarian section is the best mode of delivery in pregnant women with brain tumours, which require immediate surgery towards the term or with a viable foetus. However, risks versus benefits need to be discussed at the multidisciplinary level, and a decision must be taken that is more favourable to the mother, especially when the foetus is extremely preterm. Viability is not possible with intense premature care. Alternatively, a craniotomy can be safely performed with appropriate preparation during pregnancy under local anaesthetics and intravenous (IV) sedation. Evidence suggests that there are not any significant adverse outcomes due to surgery during pregnancy, including the cognitive development of the foetus during the immediate postnatal period.[19]

Local chemotherapy applied during surgery, such as carmustine-impregnated wafers, appears safe, but conventional chemotherapy or radiation therapy is postponed until after delivery.[13,21]

Depending on the location of the tumour, the pregnant woman's position can be sitting or lateralised, but she should avoid positions that could restrict the blood flow to the foetus. Haemodynamic parameters should be carefully monitored during surgery and kept at appropriate levels to prevent blood flow reductions in the placenta, which might cause foetal distress.[13]

It is vital to consider both the foetus and the pregnant woman's physiological changes that occur during pregnancy to determine the best mode of anaesthesia for a pregnant woman. In neurologically unstable individuals, a caesarean birth under general anaesthesia should be considered over spinal or epidural anaesthesia, followed by rapid neurosurgical decompression to limit temporal lobe or cerebellar herniation.[12] Thiopental offers a few benefits, like decreasing intracranial pressure. However, propofol, which can cross the placenta, would be a superior alternative when selecting an induction agent for maintenance during operation. Propofol, sufentanil, rocuronium, dexmedetomidine, neostigmine, and atropine have been reported to be safe during pregnancy while avoiding nitrous oxide.[2,13]

Cerebrospinal fluid (CSF) diversion (shunting and draining fluid that has built up around the brain) is one of the management options for some brain tumours. However, it is found to be a high-risk procedure for pregnant women under general anaesthesia. A colloid cyst could be aspirated stereotactically under local anaesthetic or IV sedation and is reported to be successful in pregnancy.[1]

Post-operative pain management should be carried out, considering that medications are most likely excreted in breast milk. Some brain tumours that express progesterone receptors might impact breastfeeding. Routine imaging may sometimes be required, but ionizing radiation and contrast chemicals should be minimised as they can mix with milk and can affect the foetus.[13] Apart from breastfeeding, concern should be taken regarding postpartum mental well-being, contraception, and AED dose and drug adjustment in women with brain tumours in their postpartum period.

Pre-conceptual optimisation of women with a history of brain tumours in reproductive age may be beneficial to avoid adverse maternal and foetal outcomes and reduce tumour progression and potential risks of the treatments during pregnancy.[5] Medical or surgical management of brain tumours before planning the pregnancy could improve the obstetric outcomes in this age group. However, most

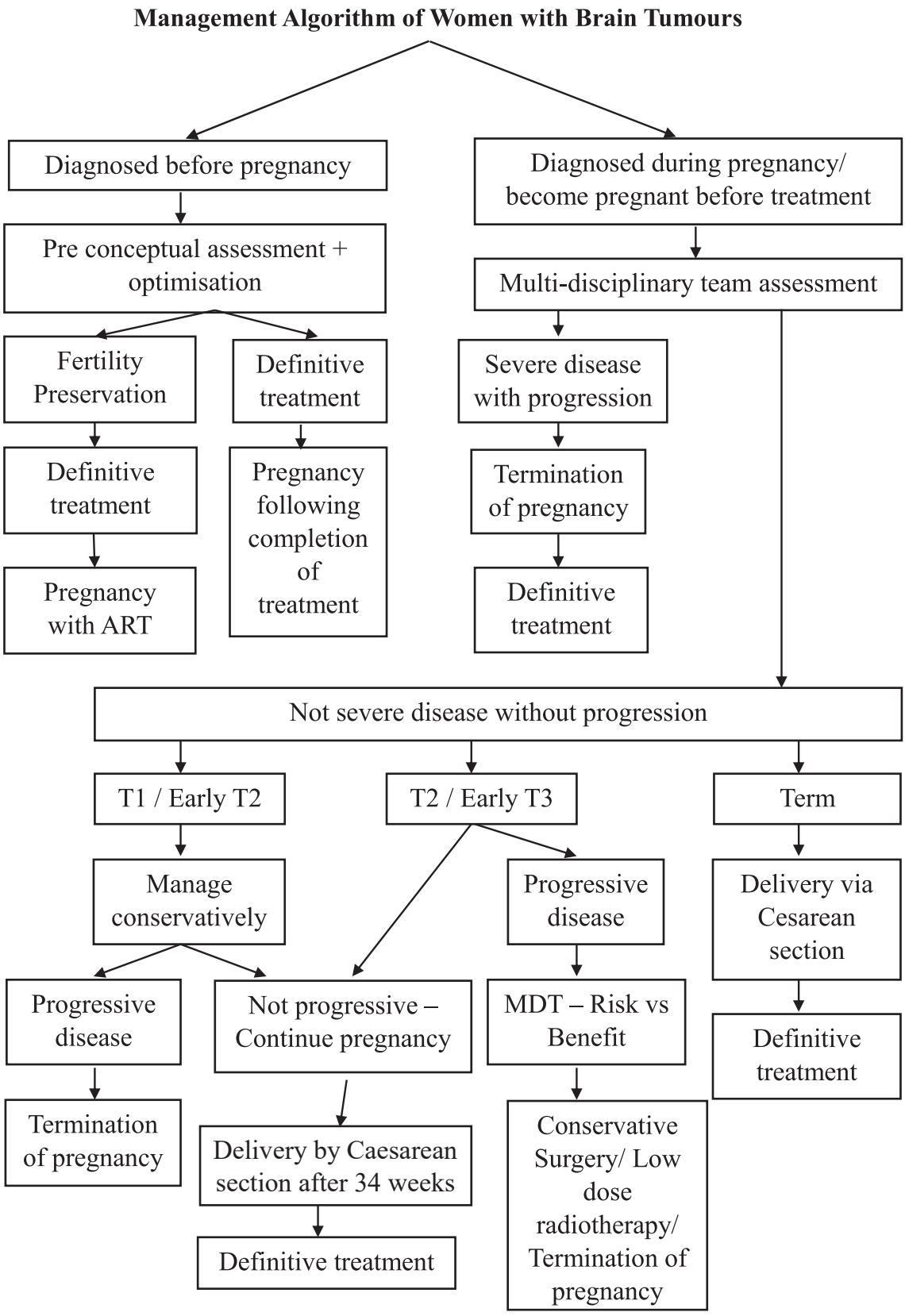

FIGURE 1. **Management algorithm of women with brain tumours.**

treatment options available for malignancy, such as chemotherapy and radiotherapy, affect fertility. Therefore, fertility preservation and counselling among these young women is a must to preserve their eggs or embryos before embarking on the treatments. This could facilitate having their biological children in future with the help of assisted reproductive technology.[23]

CONCLUSION

Pregnant women with brain tumours must be assessed and managed with multidisciplinary team inputs for better maternal and foetal outcomes while focusing on the risk versus benefits balance between the definitive treatment options. Choosing the correct diagnostic and therapeutic strategy is critical because all potential treatment options have both advantages and disadvantages in the outcome of pregnancy. However, pre-conceptual optimisation for women with brain tumours would be a promising management strategy. Counselling the pregnant woman and her relatives will support the planned management options following a comprehensive assessment.

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