Jurnal Club presentation

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Pregnancy and Family Planning in Multiple Sclerosis

INTRODUCTION

- More than 40% of women are not on treatment in the 12 months before conception and do not incur increased risk of disability.
- Accidental pregnancy exposure to some of the most commonly prescribed MS treatments in the United States, glatiramer acetate and various interferon beta preparations, appears safe.
- Breast-feeding at least briefly, even if combined with formula feedings, neither increases or decreases the risk of postpartum relapse,[1] and breast-feeding exclusively for at least 2 months postpartum appears to decrease the risk of postpartum relapses.[4] Even when

relapses occur during pregnancy or the postpartumperiod, they do not appear to affect long-term prognosis in most women.

- If treatment is needed during lactation, several medications are available that pose no biologically plausible risk to the infant if exposure occurs only via breast milk.

- the good news is there are only a few pitfalls to be avoided when managing and counseling women of childbearing potential; those with the highest impact are pregnancies that occur while a woman is still taking medications that are known to or potentially increase the risk of adverse pregnancy outcome risks and pregnancies that occur shortly after cessation of or while a woman is still taking fingolimod or natalizumab. Luckily, the large number of treatment options available now make these issues easy to avoid.

- This article also covers less common scenarios, including fertility treatment and drugs to avoid in men who desire children.

BACKGROUND

Multiple sclerosis does not increase the risk of infertility, adverse pregnancy outcomes, or adverse neonatal outcomes, but some multiple sclerosis treatments may increase these risks.

CASE 10-1

A 24-year-old woman with multiple sclerosis (MS) presented to discuss pregnancy and breast-feeding. She had been diagnosed with MS at age 20 when she presented with optic neuritis and met McDonald criteria for MS by brain MRI.

Her neurologic examination was normal.

Her brain MRI :single new non enhancing periventricular lesion since diagnosis.

She was started on a modestly effective disease modifying therapy but **stopped after 6 months**. She had not had any further relapses.

.

She was reassured that her disease was quite mild and that if a postpartum relapse occurred, it would also likely be mild and treatable like her past relapses; exclusive breast-feeding was also recommended.

In the next 3 years, she had two children and remained relapse-free and untreated. Both pregnancies were uncomplicated, both infants were breast-fed exclusively until 6 months of age. she wanted more children and was not on birth control.

Recommending this patient resume a disease-modifying therapy before or shortly after pregnancy, particularly if it meant she could not breast-feed, was not necessary as she did not have **frequent relapses, significant accumulation of new lesions on MRI, or disability from previous relapses.** Now that she may be done having children, it would be appropriate to check another **noncontrast brain MRI** to assess for lesion progression. If she has new or enlarging lesions, starting **glatiramer acetate or interferon** beta would be compatible with breast-feeding and the possibility that she may become pregnant accidentally before discontinuation of treatment.

The author recommends a risk-stratified treatment approach for all patients with MS that considers their **underlying risk of long-term disability** when deciding whether to **start or switch** to a highly effective disease-modifying therapy.

Incorporating Family Planning

in

Starting, Stopping, or Switching Multiple Sclerosis Treatments

risk factors

for

long-term disability

progressive disease course

incomplete recovery from relapses

patients with relapsing-remitting MS sphincter involvement

frequent relapses early in the disease course.

highly effective

disease modifying

therapy

relapses or unequivocally new lesions on MRI scans after **≥6** months on disease-modifying therapy.

escalating to a highly effective disease-modifying therapy

↓

alemtuzumab

Fingolimod

Natalizumab

rituximab

ocrelizumab

Mitoxantron

- Being **untreated** before and during pregnancy and during the postpartum period is seen most often in women with a history of **mild MS** disease activity, which is defined as having little to no disability, **infrequent relapses**, and **low lesion burden load on MRI**, or those who required **only modestly** effective disease-modifying therapies to control their disease activity **in the past.**

Reliable birth control

hormonal contraceptives

intrauterine device

surgical sterilization

same-sex partnership

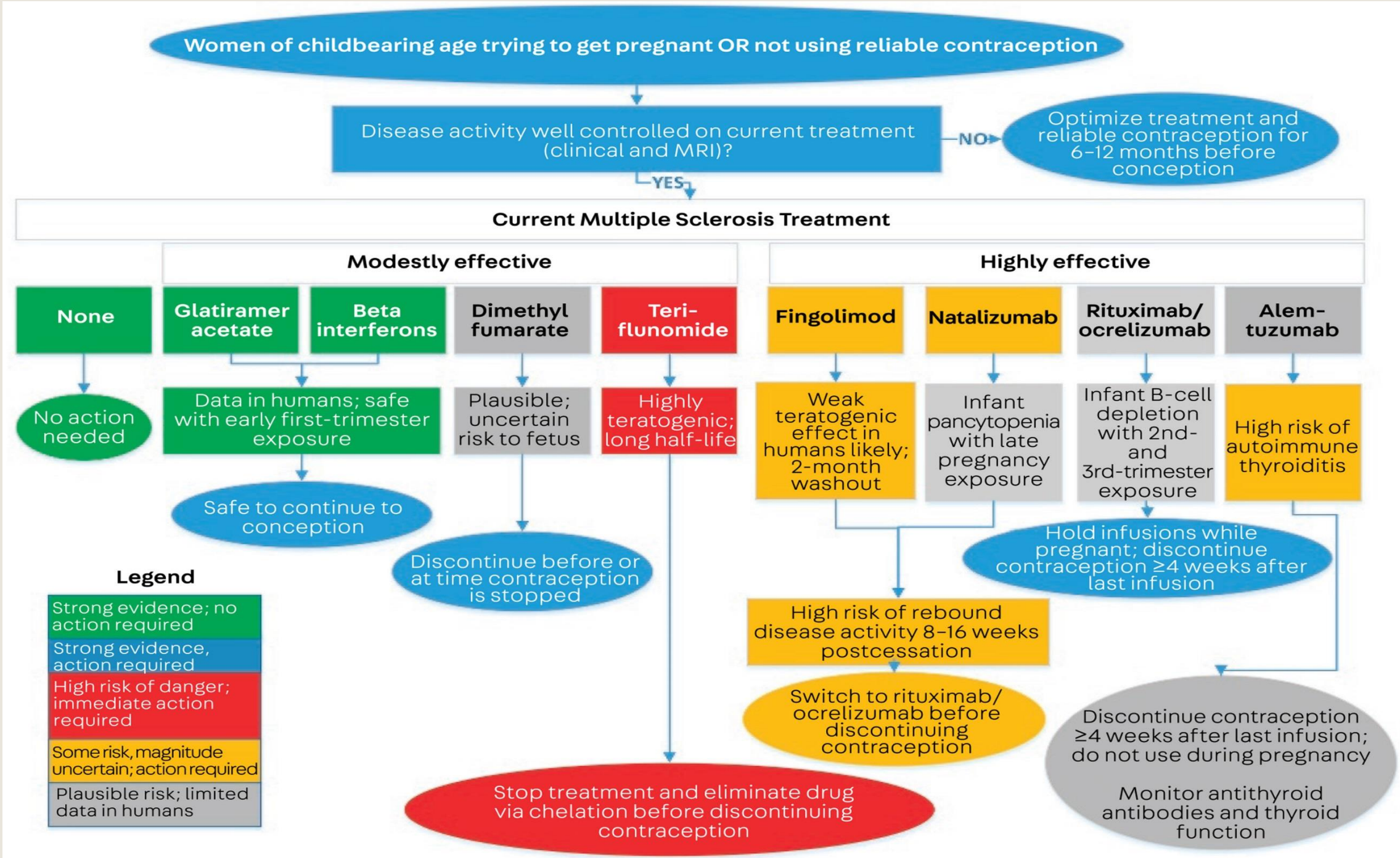
“I can’t get pregnant” if infertility is documented by an obstetrician

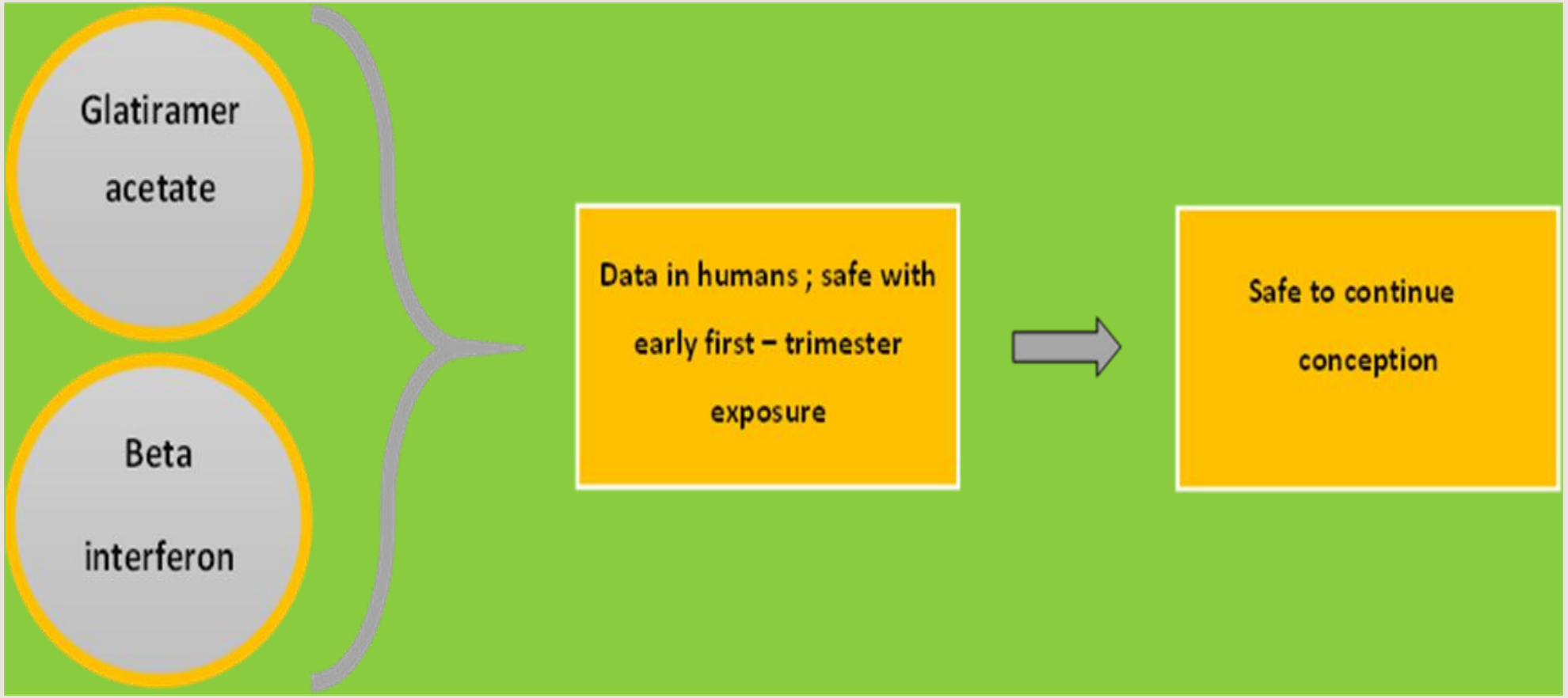
not reliable birth control

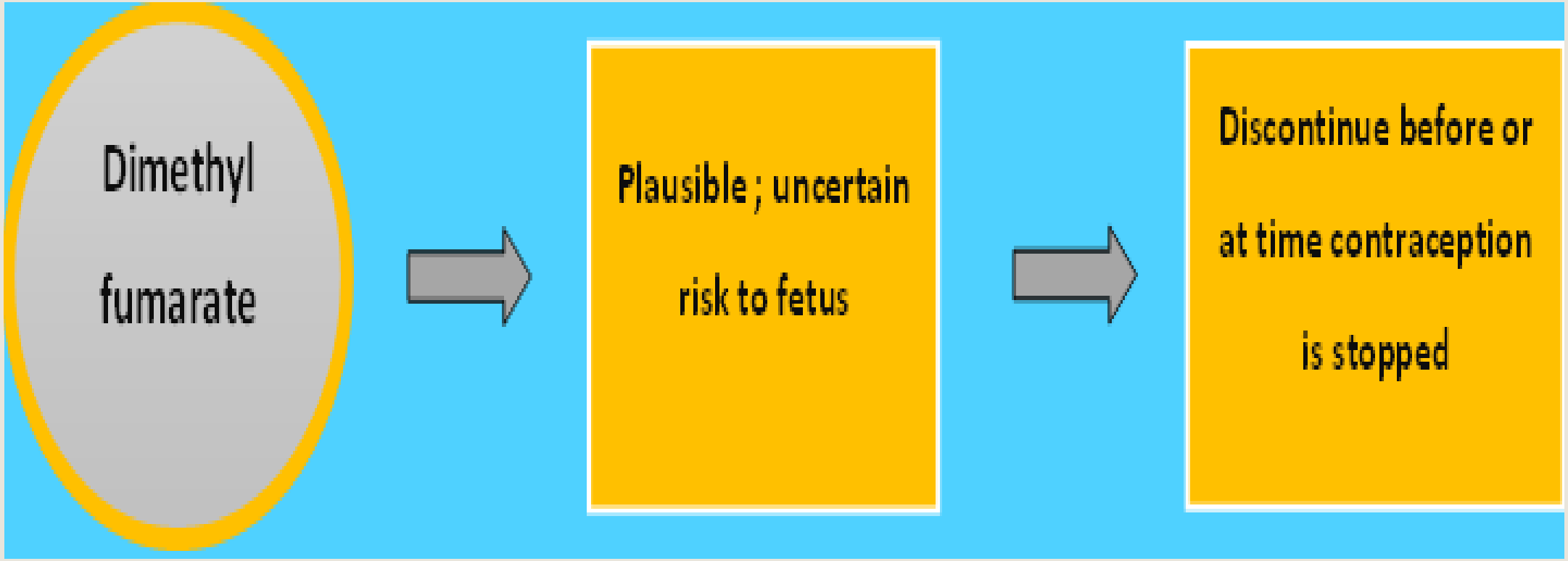
spermicide gel

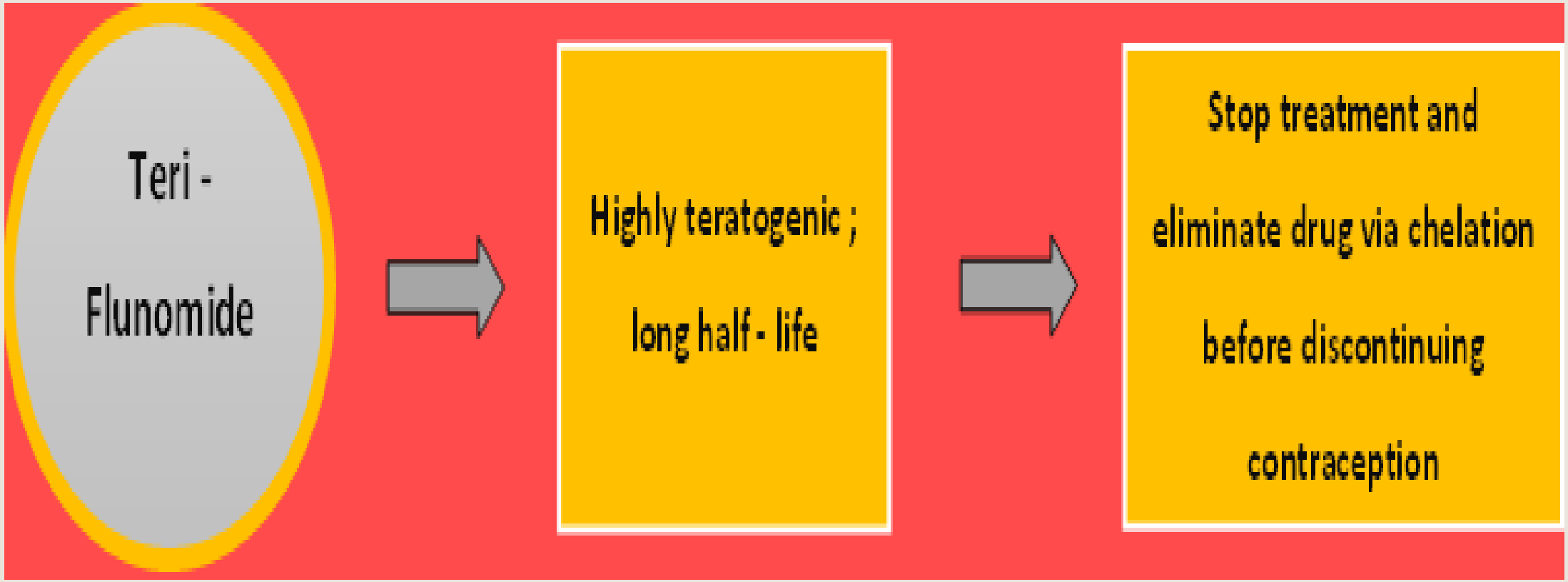
“I don’t have a boyfriend”

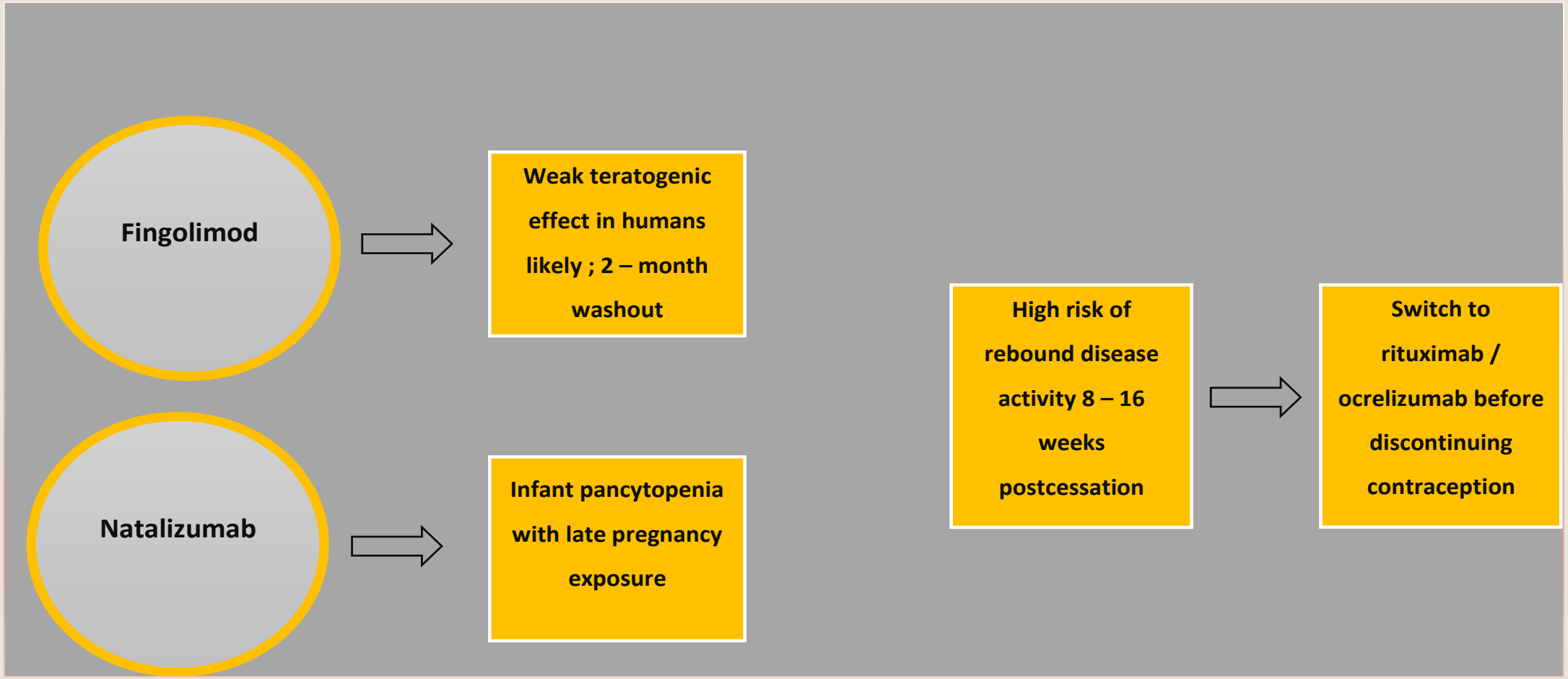
“I can’t get pregnant” (unless infertility is documented by an obstetrician

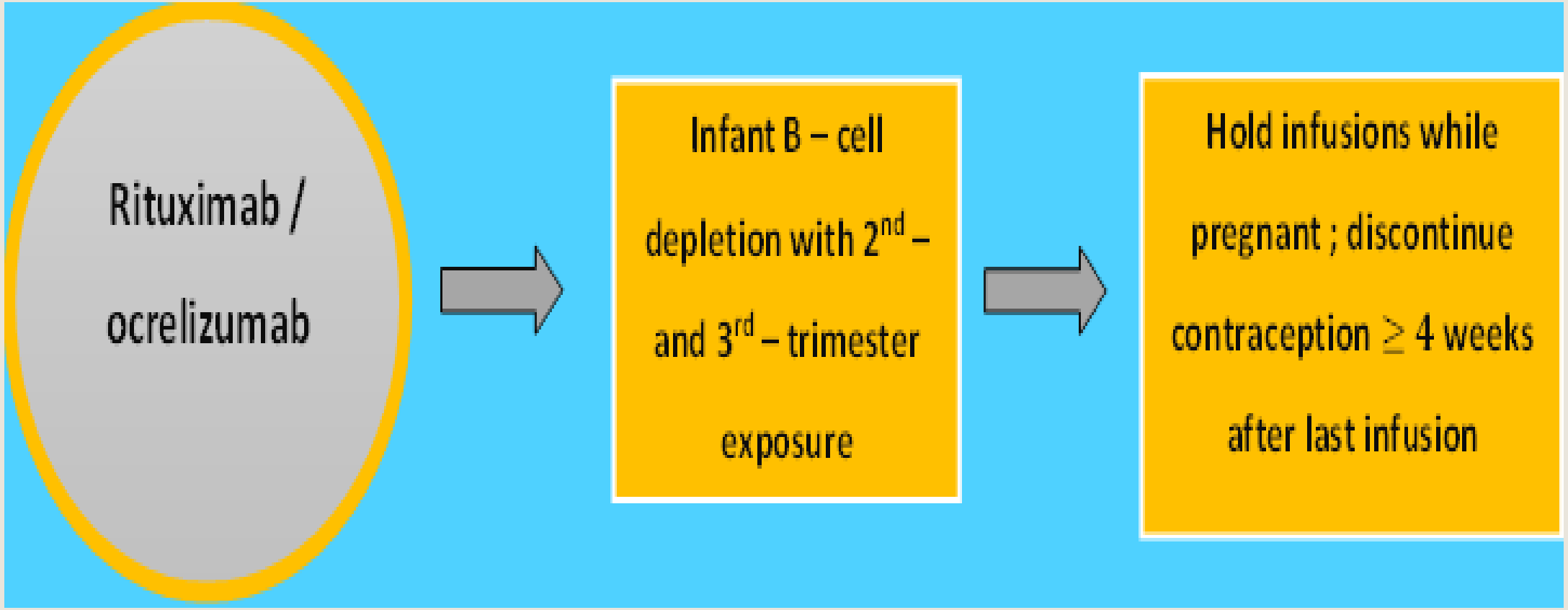

Women of childbearing age trying to get pregnant OR not using reliable contraception
Disease activity well controlled on current treatment (clinical and MRI)?
NO
Optimize treatment and reliable contraception for 6–12 months before conception
YES
Current Multiple Sclerosis Treatment
Modestly effective
Highly effective
None
Glatiramer acetate
Beta interferons
Dimethyl fumarate
Teri-flunomide
Fingolimod
Natalizumab
Rituximab/ ocrelizumab
Alem-tuzumab
No action needed
Data in humans; safe with early first-trimester exposure
Plausible; uncertain risk to fetus
Highly teratogenic; long half-life
Weak teratogenic effect in humans likely; 2-month washout
Infant pancytopenia with late pregnancy exposure
Infant B-cell depletion with 2nd- and 3rd-trimester exposure
High risk of autoimmune thyroiditis
Safe to continue to conception
Discontinue before or at time contraception is stopped
Hold infusions while pregnant; discontinue contraception ≥4 weeks after last infusion
High risk of rebound disease activity 8–16 weeks postcessation
Switch to rituximab/ ocrelizumab before discontinuing contraception
Discontinue contraception ≥4 weeks after last infusion; do not use during pregnancy
Monitor antithyroid antibodies and thyroid function
Stop treatment and eliminate drug via chelation before discontinuing contraception
Legend
Strong evidence; no action required
Strong evidence, action required
High risk of danger; immediate action required
Some risk, magnitude uncertain; action required
Plausible risk; limited data in humans

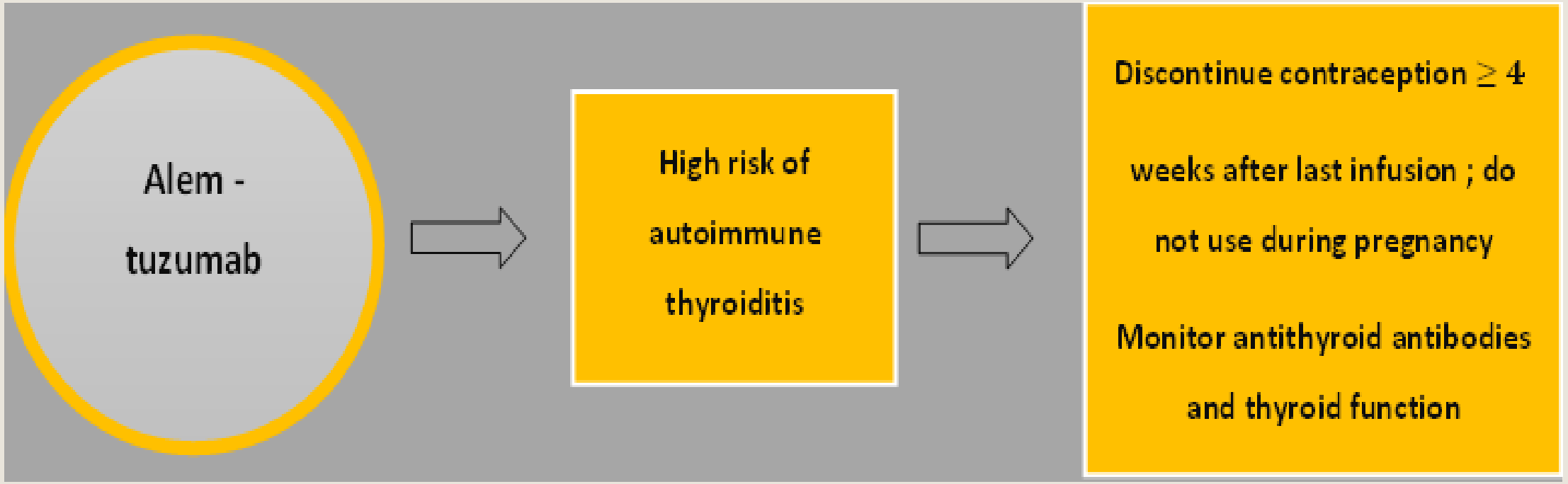

Glatiramer acetate
Beta interferon
Data in humans ; safe with early first – trimester exposure
Safe to continue conception


Dimethyl fumarate
Plausible ; uncertain risk to fetus
Discontinue before or at time contraception is stopped


Teri -
Flunomide
Highly teratogenic ;
long half - life
Stop treatment and
eliminate drug via chelation
before discontinuing
contraception


Fingolimod
Weak teratogenic effect in humans likely ; 2 – month washout
Natalizumab
Infant pancytopenia with late pregnancy exposure
High risk of rebound disease activity 8 – 16 weeks postcessation
Switch to rituximab / ocrelizumab before discontinuing contraception

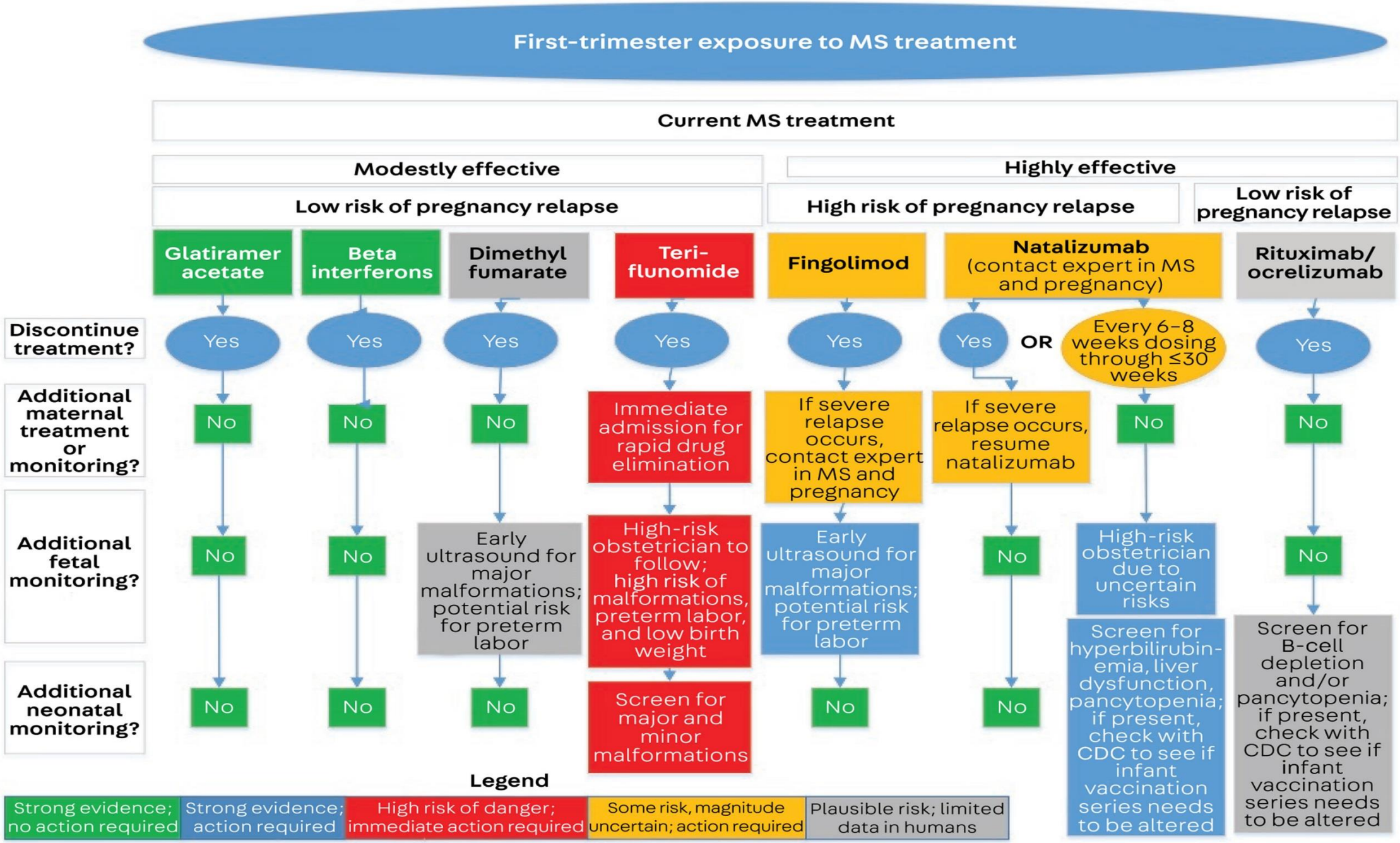

Rituximab / ocrelizumab
Infant B – cell depletion with 2nd – and 3rd – trimester exposure
Hold infusions while pregnant ; discontinue contraception ≥ 4 weeks after last infusion

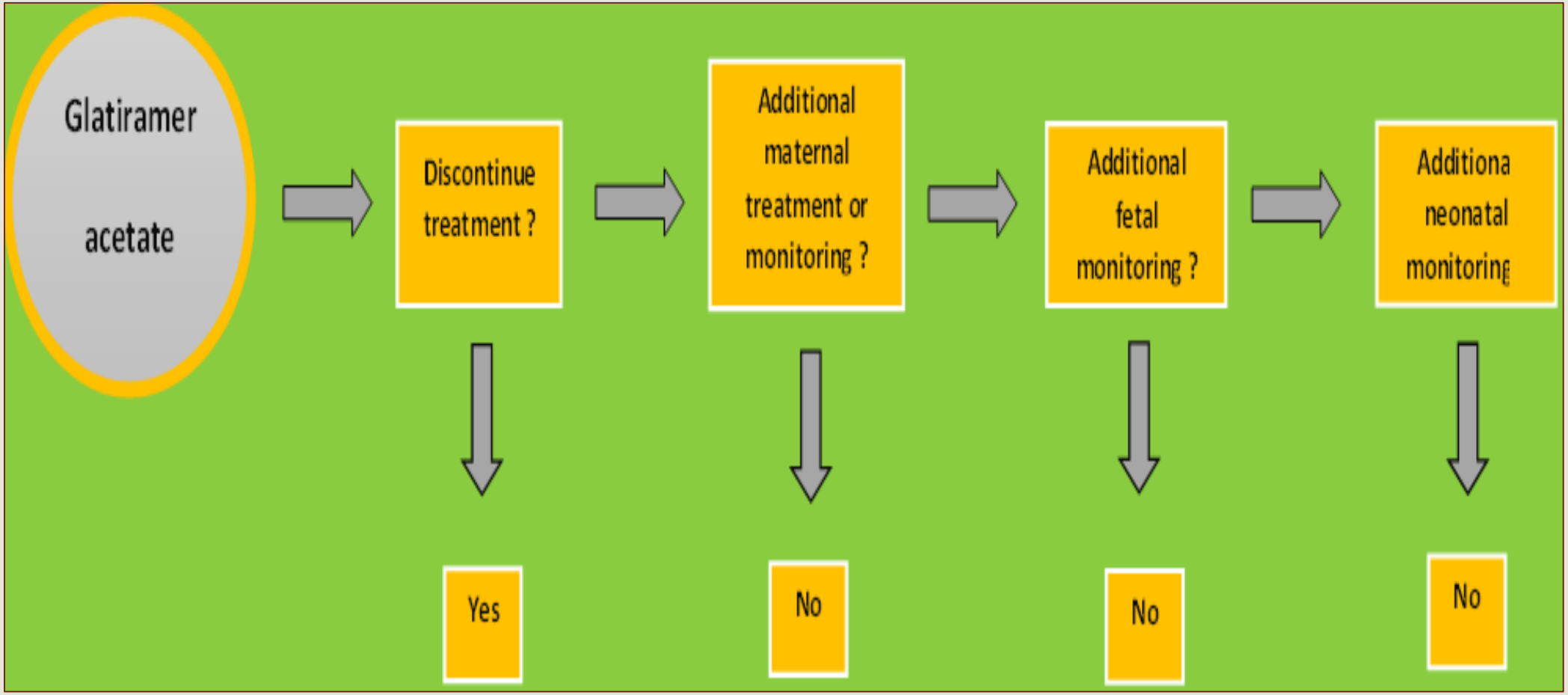

Alem - tuzumab
High risk of autoimmune thyroiditis
Discontinue contraception ≥ 4 weeks after last infusion ; do not use during pregnancy
Monitor antithyroid antibodies and thyroid function

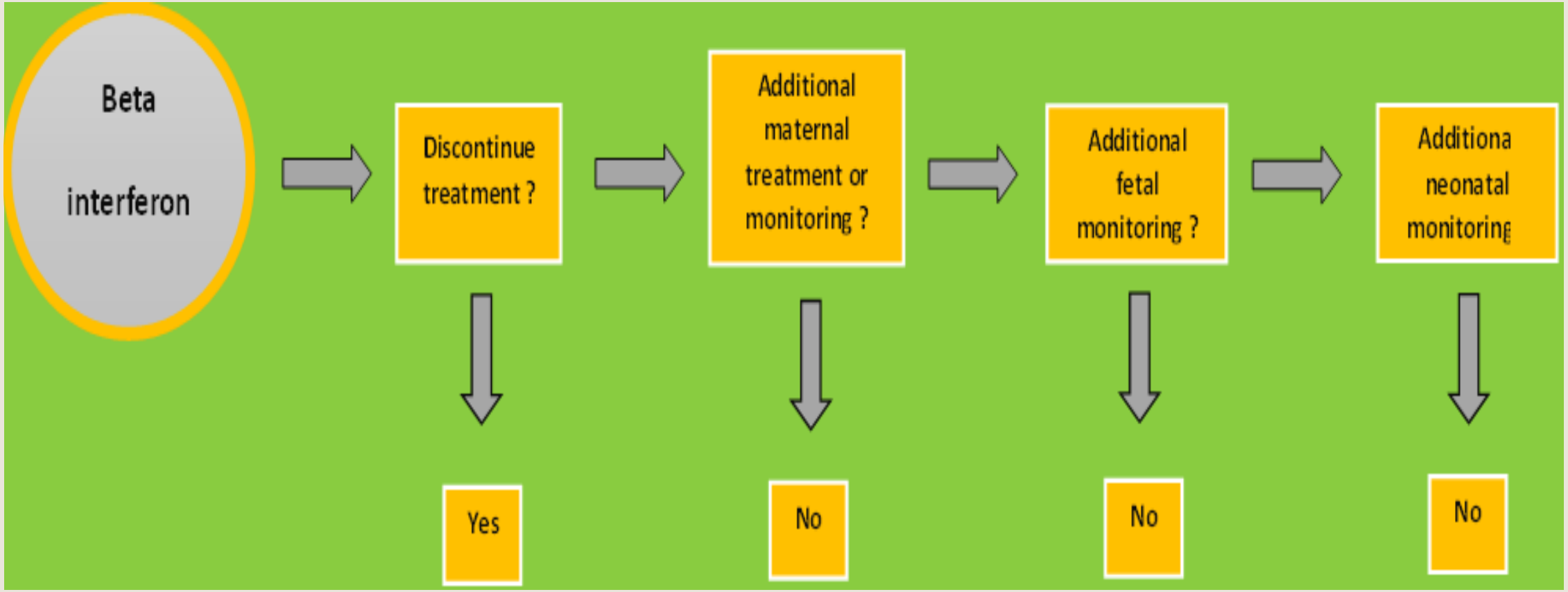
women will opt to start reliable birth control so they can take an **oral disease-modifying therapy or natalizumab**.

checking to make sure they are refilling their contraceptive prescriptions at the same time they request refills on their oral disease modifying

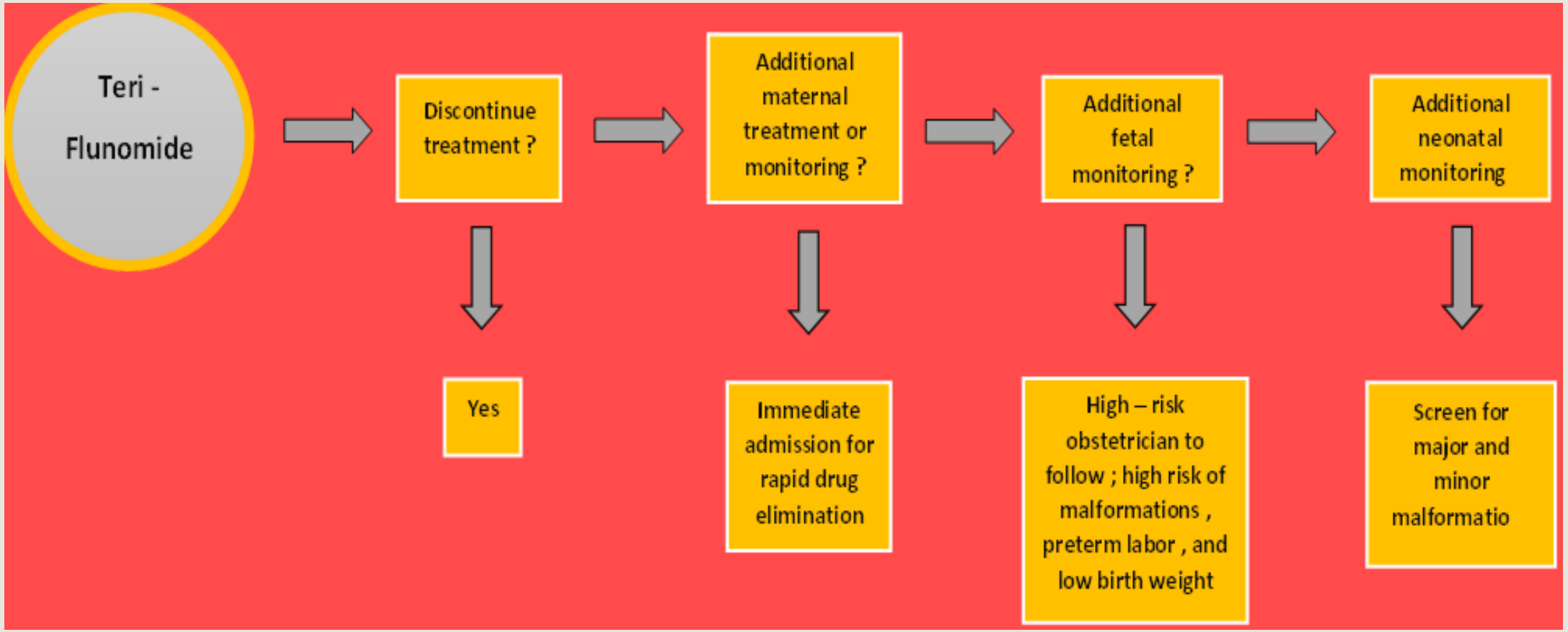
therapies, in addition to inquiring at clinic visits

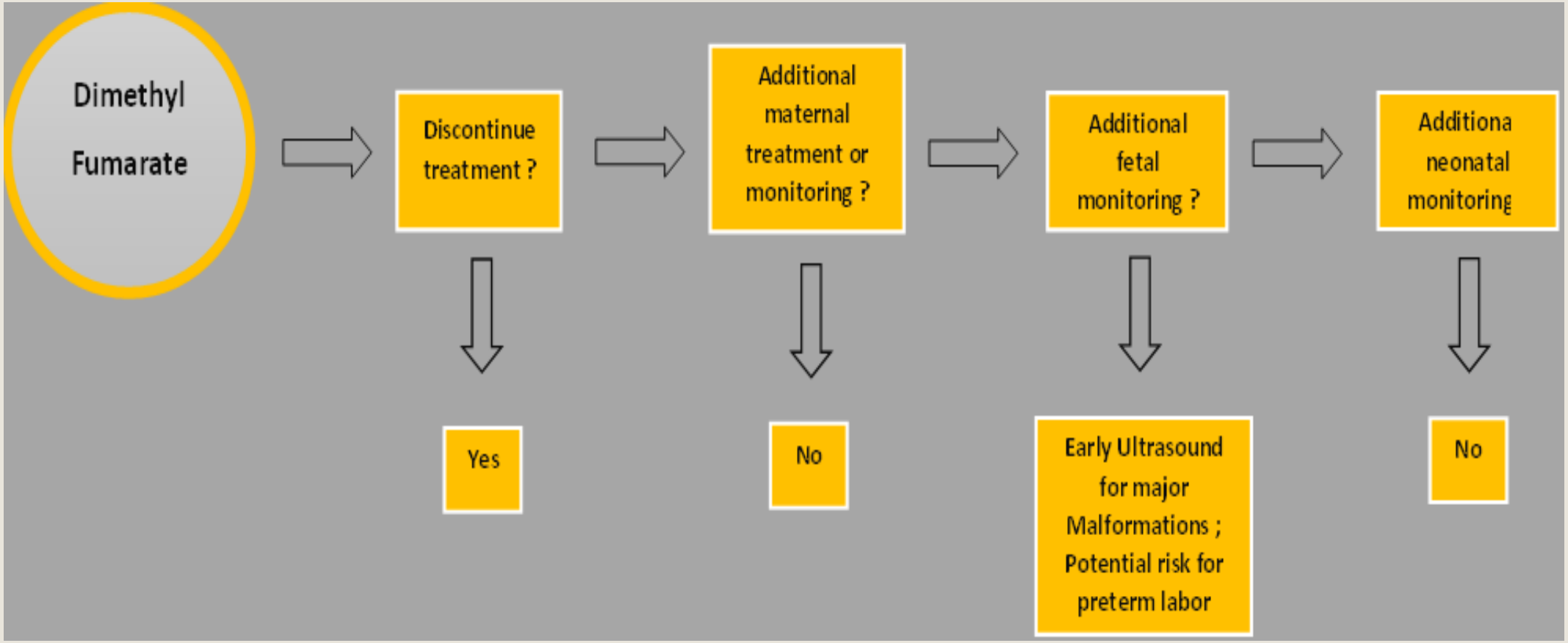

First-trimester exposure to MS treatment
Current MS treatment
Modestly effective
Highly effective
Low risk of pregnancy relapse
High risk of pregnancy relapse
Low risk of pregnancy relapse
Glatiramer acetate
Beta interferons
Dimethyl fumarate
Teri-flunomide
Fingolimod
Natalizumab (contact expert in MS and pregnancy)
Rituximab/ ocrelizumab
Discontinue treatment?
Yes
Yes
Yes
Yes
Yes
Yes
OR
Every 6–8 weeks dosing through ≤30 weeks
Yes
Additional maternal treatment or monitoring?
No
No
No
Immediate admission for rapid drug elimination
If severe relapse occurs, contact expert in MS and pregnancy
If severe relapse occurs, resume natalizumab
No
No
Additional fetal monitoring?
No
No
Early ultrasound for major malformations; potential risk for preterm labor
High-risk obstetrician to follow; high risk of malformations, preterm labor, and low birth weight
Early ultrasound for major malformations; potential risk for preterm labor
No
High-risk obstetrician due to uncertain risks
No
Additional neonatal monitoring?
No
No
No
Screen for major and minor malformations
No
No
Screen for hyperbilirubin-emia, liver dysfunction, pancytopenia; if present, check with CDC to see if infant vaccination series needs to be altered
Screen for B-cell depletion and/or pancytopenia; if present, check with CDC to see if infant vaccination series needs to be altered
Legend
Strong evidence; no action required
Strong evidence; action required
High risk of danger; immediate action required
Some risk, magnitude uncertain; action required
Plausible risk; limited data in humans

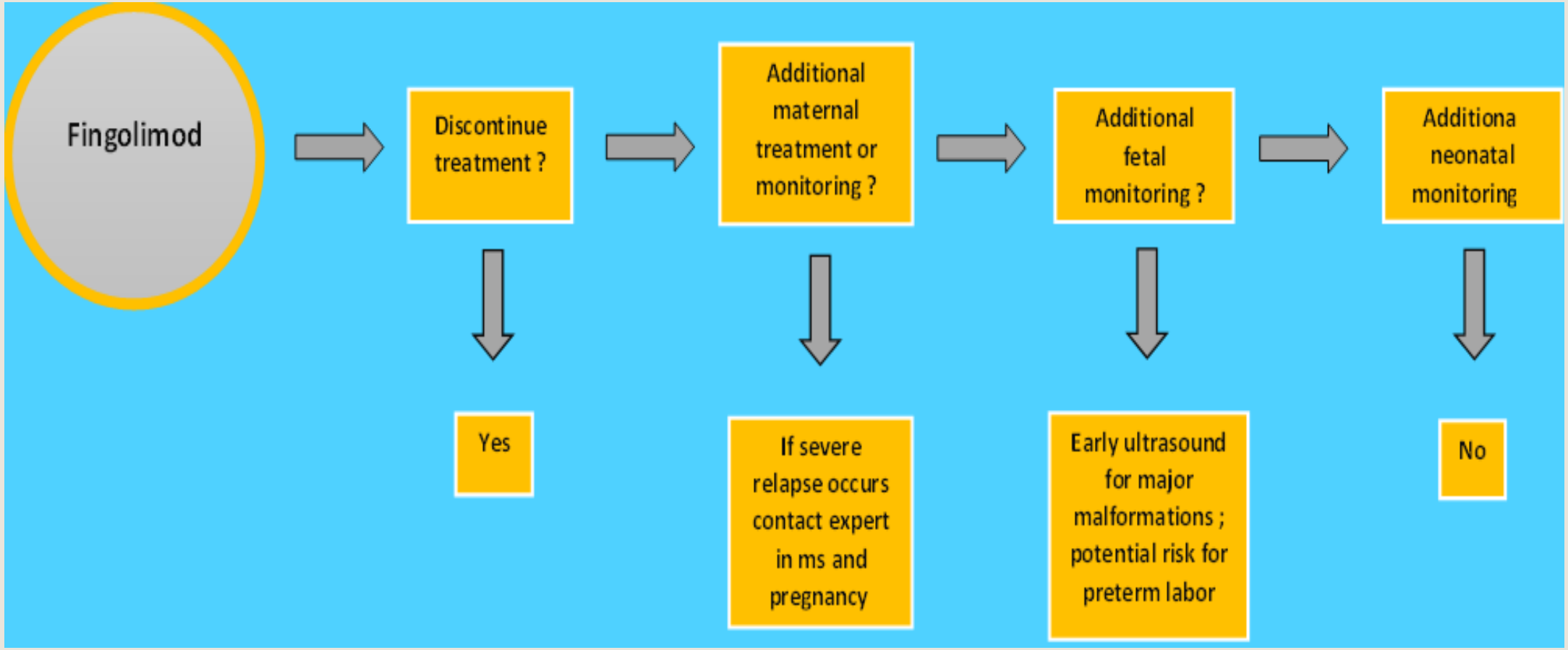

Glatiramer acetate
Discontinue treatment ?
Additional maternal treatment or monitoring ?
Additional fetal monitoring ?
Additiona neonatal monitoring
Yes
No
No
No

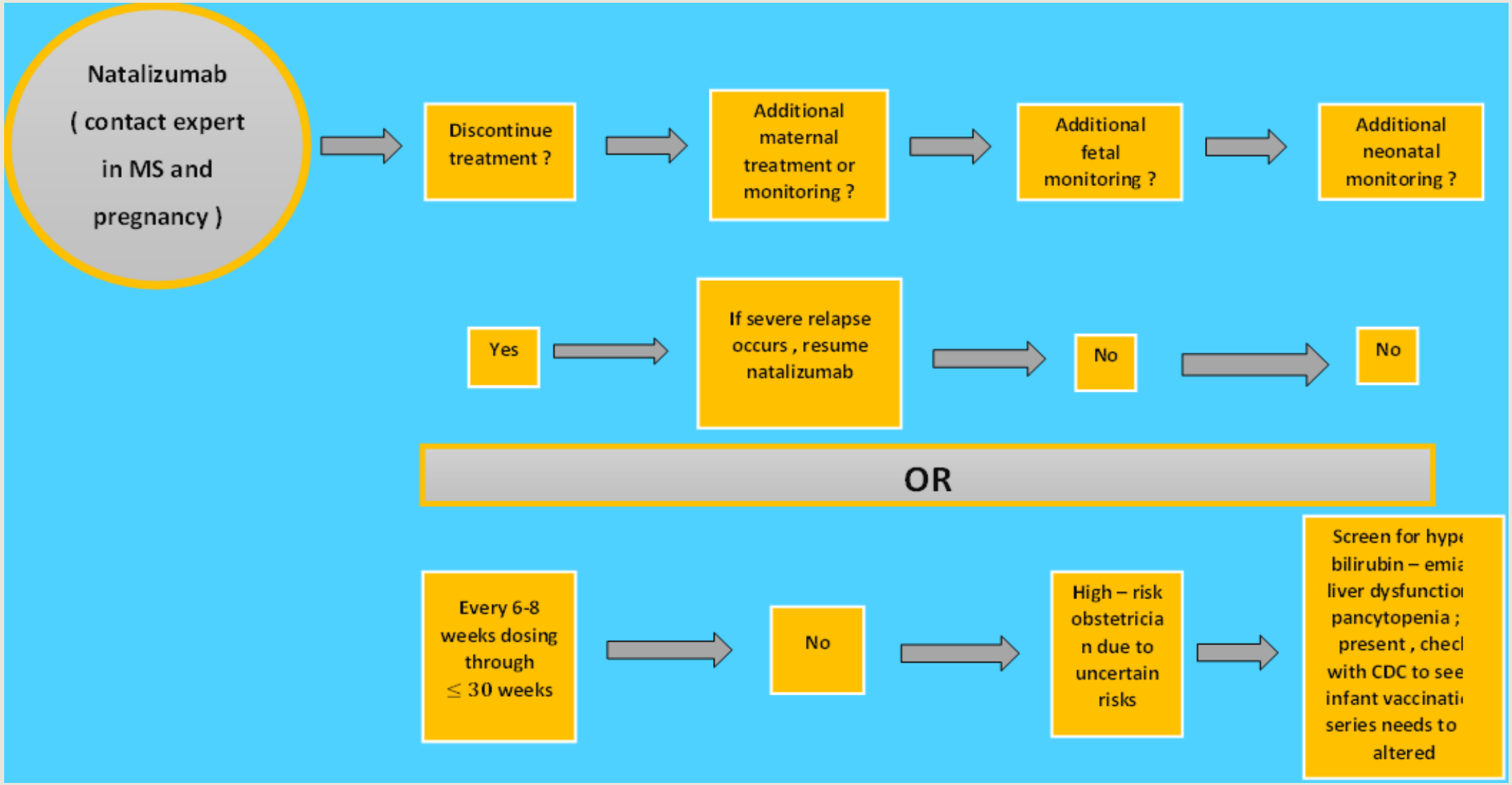

Beta interferon
Discontinue treatment ?
Additional maternal treatment or monitoring ?
Additional fetal monitoring ?
Additiona neonatal monitoring
Yes
No
No
No

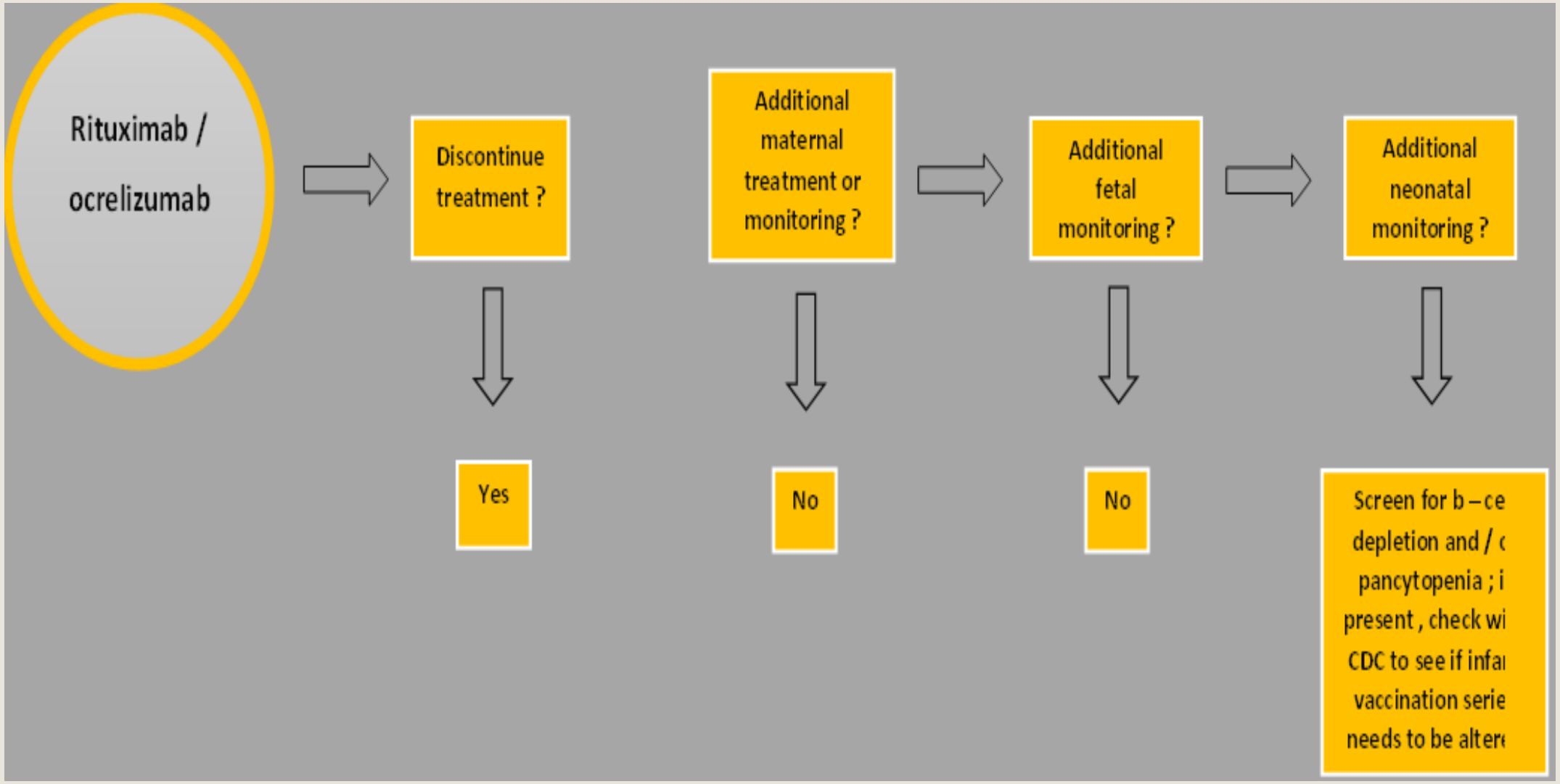
No disease-modifying therapy has been shown to be safe for use **throughout pregnancy.**


Teri - Flunomide
Discontinue treatment ?
Yes
Additional maternal treatment or monitoring ?
Immediate admission for rapid drug elimination
Additional fetal monitoring ?
High – risk obstetrician to follow ; high risk of malformations , preterm labor , and low birth weight
Additional neonatal monitoring
Screen for major and minor malformatio


Dimethyl Fumarate
Discontinue treatment ?
Yes
Additional maternal treatment or monitoring ?
No
Additional fetal monitoring ?
Early Ultrasound for major Malformations ; Potential risk for preterm labor
Additiona neonatal monitoring
No


Fingolimod
Discontinue treatment ?
Additional maternal treatment or monitoring ?
Additional fetal monitoring ?
Additiona neonatal monitoring
Yes
If severe relapse occurs contact expert in ms and pregnancy
Early ultrasound for major malformations ; potential risk for preterm labor
No


Natalizumab (contact expert in MS and pregnancy)
Discontinue treatment ?
Additional maternal treatment or monitoring ?
Additional fetal monitoring ?
Additional neonatal monitoring ?
Yes
If severe relapse occurs , resume natalizumab
No
No
OR
Every 6-8 weeks dosing through ≤ 30 weeks
No
High – risk obstetrician due to uncertain risks
Screen for hype bilirubin – emia liver dysfunctio pancytopenia ; present , chec with CDC to see infant vaccinati series needs to altered


Rituximab / ocrelizumab
Discontinue treatment ?
Yes
Additional maternal treatment or monitoring ?
No
Additional fetal monitoring ?
No
Additional neonatal monitoring ?
Screen for b – ce
depletion and / c
pancytopenia ; i
present , check wi
CDC to see if infa
vaccination serie
needs to be alter

rituximab

In women who require a highly effective disease-modifying therapy to control their disease while trying to get pregnant or not on reliable birth control, rituximab is the author’s preferred **choice**.

clinical experience in Sweden showed that a 500 mg maintenance dose was equally effective and safer than 1000 mg every 6 months.

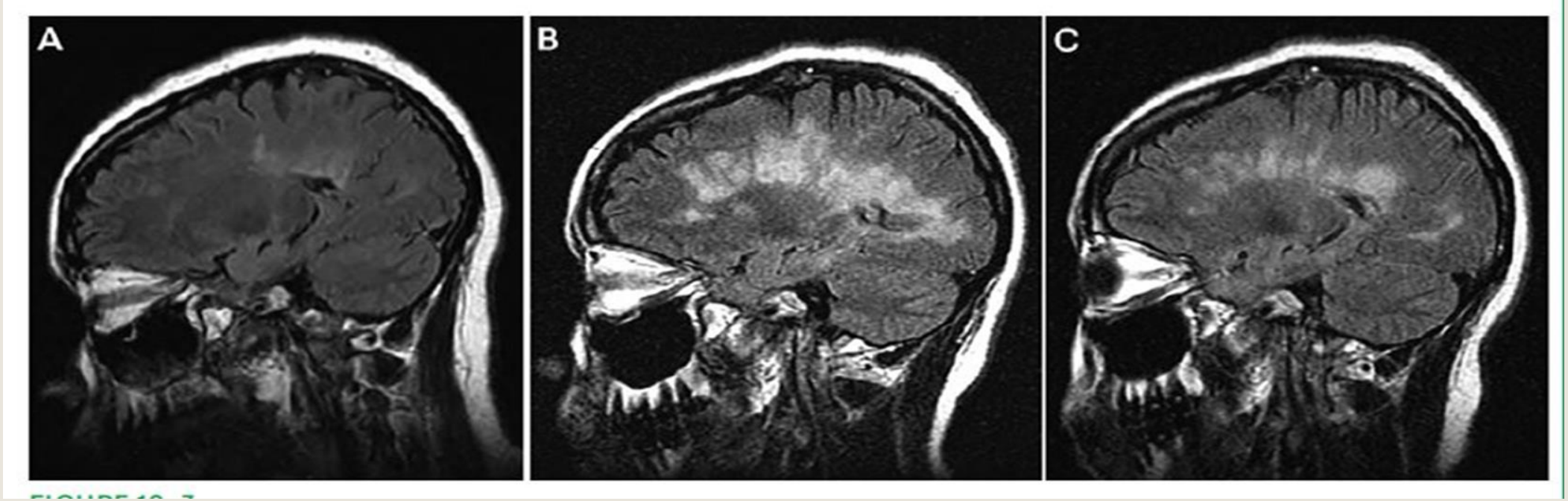
the author recommends waiting **1 month** after each infusion to ensure that the drug is cleared before placental transfer begins in the second trimester, although should a woman become pregnant even within **1 week** after the last infusionn, there is no cause for alarm.

NATALIZUMAB

CASE 10-2

A 26-year-old woman with relapsing-remitting multiple sclerosis (MS) presented in follow-up. She had been diagnosed with MS at the age of 18; multiple **modestly effective** disease-modifying therapies were prescribed but failed to control her MS, and she had frequent relapses and new lesions on MRI. At age 20, she was started on. **Natalizumab** After 2 years of being relapse-free and having no new lesions on MRI. She accidentally became pregnant. Natalizumab was stopped, with her last dose at approximately 8 to 10 weeks of gestation.

During the late second trimester (**4.5 months** after her last dose of natalizumab), she had a relapse with significant **unilateral leg weakness** requiring her to use a cane. She was treated with IV methylprednisolone with some improvement; this was the most severe relapse she had ever had. In her early third trimester **(1 month later),** she had a second pregnancy relapse **(optic neuritis)** that was treated with IV methylprednisolone with complete resolution. She had a normal labor and delivery.



- **A**, Prepregnancy; MRI shows minimal
- signs and the patient had no disability and an Expanded Disability Status Scale (EDSS) score of 1.5.

- **B**, 1 Month postpartum; the patient had unilateral leg weakness and an EDSS score of 4.0.

- **C**, 10 Months postpartum; the patient had fatiguing leg weakness and an EDSS score of 2.5.

- Her baby had normal Apgar scores but was small for gestational age. She resumed natalizumab within 2 weeks following delivery and remained relapse-free. She breast-fed for only 3 weeks

Natalizumab exposure during early pregnancy does not appear to be fetotoxic and should not be a cause for alarm.

The expert may recommend continuing natalizumab at to 6-8week extended intervals, with the last dose occurring at less than 30 weeks, or stopping it.

plasma exchange

resuming natalizumab

starting rituximab

Starting ocrelizumab

Starting alemtuzumab

Severe

steroid-refractory

rebound relaps

treating relapses during pregnancy with high-dose corticosteroid infusions, resuming natalizumab, or starting rituximab all appear to carry higher risks than prepregnancy exposure to rituximab.

he author recommends stopping natalizumab or fingolimod and continuing contraception until the risk of rebound relapse has passed (6 to 12months) before trying to conceive

FDA : breast-feeding is not recommended while the patient is on any disease-modifying therapy.

the author never recommends the use of oral disease-modifying therapies during breast-feeding.

Exclusive breast-feeding appears to reduce the risk of postpartum MS activity

resuming disease-modifying therapies would reduce the risk of relapses in the early postpartum period

Disease-Modifying Therapy	Description	Detectable in Breast Milk?	Transluminal Transfer?[a]	Expected Effects With Infant Exposure[b]	Compatible With Lactation?
Large moleculeas					
Glatiramer acetate	Large molecule (4.7–13 kDa) heterogeneous strings of amino acids	Not done, unlikely	Yes, as with any amino acid	None	Yes
Interferon beta	Large molecule, protein	۰٫۰۰۰۶٪ relative infant dose	Exceedingly low	Flulike symptoms	Yes

Disease Modifying Therapy	Description	Detectable in Breast Milk?	Transluminal Transfer?[a]	Expected Effects With Infant Exposure[b]	Compatible With Lactation?
Monoclonal antibodies				Infections,[c] impaired vaccine responses or disseminated disease from live vaccines,[c] hepatitis,[c] anemia[c]	
Natalizumab	IgG4	<1:200 of maternal serum level; 2–5% relative infant dose	Exceedingly low		Yes, if needed
Rituximab	IgG1	Approximately ١:٢٤٠ of maternal serum level	Exceedingly low	B-cell depletion, infections,[c] impaired vaccine responses or disseminated disease from live vaccines[c]	Yes, if needed

Disease-Modifying Therapy	Description	Detectable in Breast Milk?	Transluminal Transfer?[a]	Expected Effects With Infant Exposure[b]	Compatible With Lactation?
Small molecules					
Dimethyl fumarate	Immediately metabolized to monomethyl fumarate (129 Da), low protein binding	Animals yes/ humans not done but highly likely in high amounts	High	Neurocognitive impairment, lymphopenia, gastrointestinal upset, infections,[c] vaccine responses[c]	No
Fingolimod	Highly protein bound, long half-life	Animals yes/ humans not done but highly likely in low amounts	Moderate	Infections,[c] vaccine responses,[c] cardiovascular effects,[c] pulmonary toxicity,[c] hepatitis[c]	No
Teriflunomide	Inhibits pyrimidine synthesis, highly protein bound, very long half life	Animals yes/ humans not done but highly likely	High	Pancytopenia, infections, vaccine responses,[c] hepatotoxicity, later-life neoplasms[c]	No

TREATING RELAPSES DURING PREGNANCY OR BREAST-FEEDING

- Very small amounts of methylprednisolone are detectable in breast milk, declining rapidly within 12 hours after infusion; thus, it is not necessary to stop breast-feeding. The author advises women to wait 3 to 4 hours after completion of the infusion before nursing or, for the very risk averse, to “pump and dump” for 24 hours after infusions.

MRI AND GADOLINIUM USE DURING PREGNANCY AND LACTATION

MRI is safe, even in the first trimester, **but** gadolinium at any time during pregnancy is not.

most professional societies to conservatively recommend pumping and dumping for **24 hours** after infusion when gadolinium administration is required during lactation..

SAFE

tricyclic antidepressants

selective serotonin reuptake inhibitors

Gabapentin

caffeine

should be avoided

valproate

Topiramate

methylphenidate

amphetamines

modafinil

carbamazepine

baclofen

Modafinil but not disease-modifying therapies, may decrease the effectivenes of hormonal contraceptives.

FERTILITY TREATMENTS AND MULTIPLE SCLEROSIS

gonadotropin-releasing hormone agonists (as opposed to antagonists) may increase risk of relapse.

For women who require treatment with MS disease-modifying therapies during prolonged periods of fertility treatments, the author usually recommends glatiramer acetate or, if a highly effective treatment is needed, rituximab.

the FDA recommends that males taking

teriflunomide should use effective contraception.

marijuana use

Hypothalamic involvement

Thanks for Your Attention