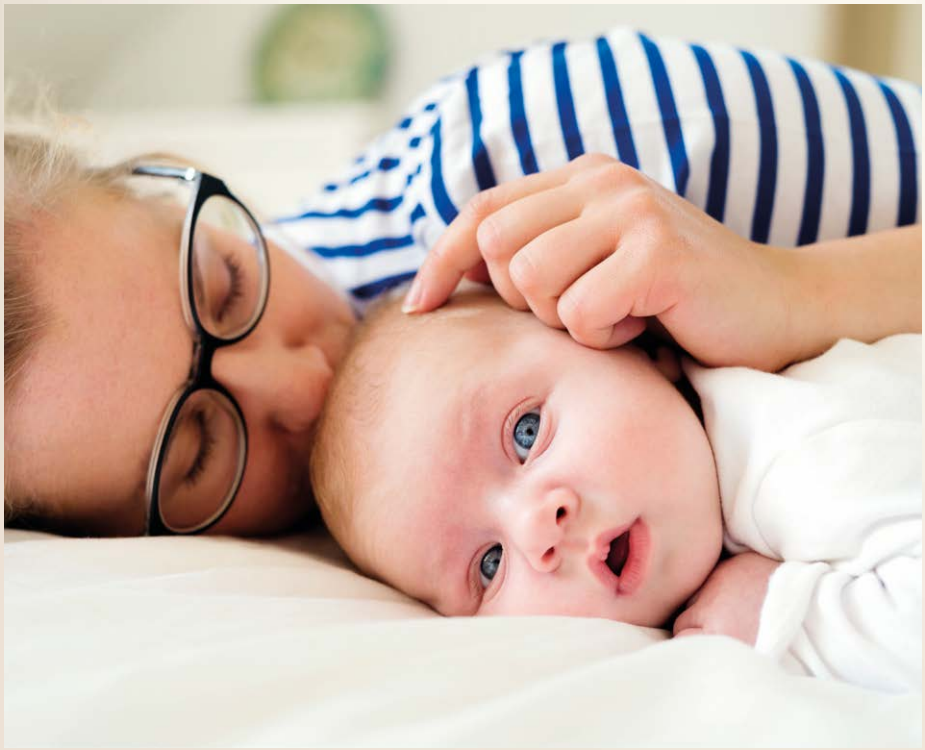
Interview

Betaferon® and Pregnancy

INTERVIEW WITH DR. GIROLAMA ALESSANDRA MARFIA

MS and pregnancy: The importance of proactive counseling

Find out more in the interview with
Dr. Girolama Alessandra Marfia inside this issue.



EDITORIAL

The typical multiple sclerosis (MS) patient is a woman of childbearing age. Therefore, not surprisingly, pregnancy is a major concern for many MS patients and they expect proactive counseling from their neurologist before, during and after the pregnancy.

In this series of articles we present the viewpoints of MS experts from around the world on the practical management of pregnancy and pregnancy-related topics for patients with MS. In this issue, Dr. Girolama Alessandra Marfia from Italy, highlights the importance of proactive counseling of patients with MS on all aspects around MS and pregnancy as well as the importance of interdisciplinary collaboration.

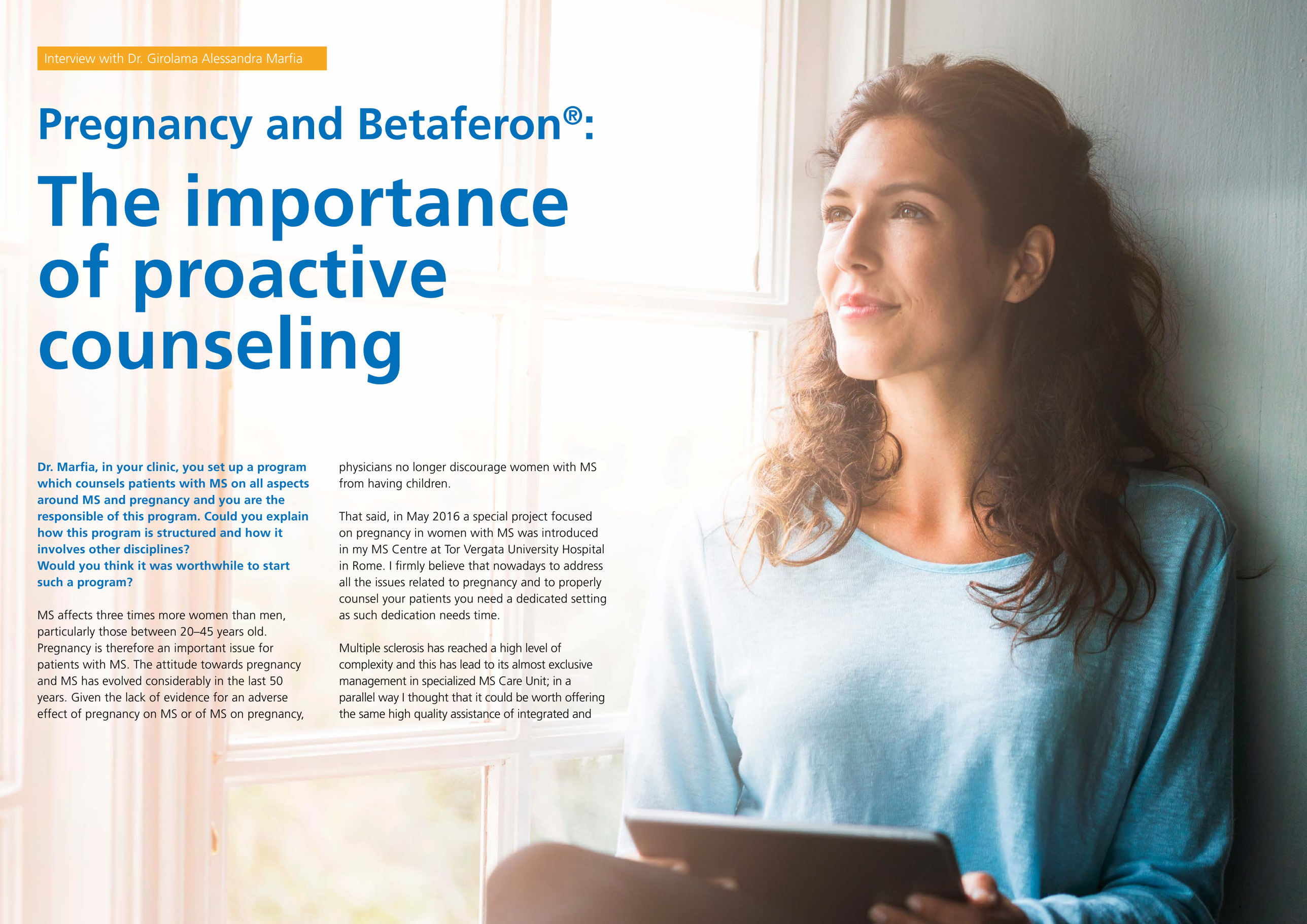
Patrick Salonis
Bayer U.S. LLC,
Global and US Brand Director, Betaferon®

BETAFERON®
Interferon beta-1b

Interview with Dr. Girolama Alessandra Marfia

Pregnancy and Betaferon®:

The importance of proactive counseling



Dr. Marfia, in your clinic, you set up a program which counsels patients with MS on all aspects around MS and pregnancy and you are the responsible of this program. Could you explain how this program is structured and how it involves other disciplines?
Would you think it was worthwhile to start such a program?

MS affects three times more women than men, particularly those between 20–45 years old. Pregnancy is therefore an important issue for patients with MS. The attitude towards pregnancy and MS has evolved considerably in the last 50 years. Given the lack of evidence for an adverse effect of pregnancy on MS or of MS on pregnancy, physicians no longer discourage women with MS from having children.

That said, in May 2016 a special project focused on pregnancy in women with MS was introduced in my MS Centre at Tor Vergata University Hospital in Rome. I firmly believe that nowadays to address all the issues related to pregnancy and to properly counsel your patients you need a dedicated setting as such dedication needs time.

Multiple sclerosis has reached a high level of complexity and this has lead to its almost exclusive management in specialized MS Care Unit; in a parallel way I thought that it could be worth offering the same high quality assistance of integrated and

multidisciplinary care to MS patients who desire motherhood. Nowadays it is well known that pregnancy is feasible for women with MS and that such a pregnancy is not at risk. Nevertheless, the peripregnancy period represents in most of the cases a challenge as there are some specific issues that need to be addressed, in particular the mother's disease history, her annual relapse rate and degree of disability and the disease-modifying drug the woman is taking.

Proactive counseling should be encouraged also in order to alleviate the fears and concerns of the patient: MS patients want to know what to expect before, during and after pregnancy and have lots of pressing questions about pregnancy outcomes, baby's health and probability of transmitting the disease to the child.

> **Proactive counseling should be encouraged also in order to alleviate the fears and concerns of the patient.**

Physicians are now encouraged to counsel patients at every opportunity, and throughout the family planning process. Therefore, clinicians should be properly trained and constantly updated. As many medications are on the market and not all of them are compatible with conception, family planning became more and more urgent.

To answer all these unmet needs we have created a MS Pregnancy Unit. In particular, we started a family planning clinic attended by women who are planning pregnancy, who are already pregnant or are in the postpartum stage until the baby is one year old. The consultancy takes place every fortnight in the afternoon to facilitate the couple and in this setting time is not limited so that all the different pregnancy-related issues could be faced and discussed with the patient and her partner.

We strictly collaborate with gynecologists who dedicate a specific surgery to our MS patients. We work as a team sharing common objectives and discussing the most complex cases during interdisciplinary periodic meetings. A link with infertility specialists has also been realized. In the network other specialists like anesthesiologists, neonatologists, psychologists and immunologists are involved. Constant communication between multidisciplinary teams is promoted. Moreover we actively collaborate with MS patients association to implement projects in the field of social care. Another relevant aim of our initiative is to promote an educational program for patients and neurologists and also for other important professional figures such as psychologists, midwives and physiotherapists who can be relevant supportive figures during the delicate time of postpartum. So far more than eighty women have been followed in our program.

In the US, pregnancy rates among people with MS are on the rise. A recent study in Italy reported that younger females with milder forms of MS are more in favor of having a child than patients with more severe disease courses. What are the observations in your consultancies?

Although MS was reported to be associated with a higher frequency of childlessness, we know from recent published data that the general trend in the United States and not only there, is that women with MS are more likely to get pregnant now. Pregnancy rates in MS female population have increased in the last decades in contrast to the downslope observed in healthy women.

These data probably reflect, on one hand, the improvement in our knowledge of the reciprocal influences between pregnancy and MS and on the other hand an improvement in our patient level of health and wellness with reduced experienced disability as a result of the introduction of innovative therapeutic strategies. Both these aspects make our patients more prone to experience motherhood.

In our population of almost 2000 MS patients in less than three years we cared for more than 80 pregnancies and the median EDSS of our patients was effectively quite low, about 75% of the patients who become pregnant have EDSS below 2.0. In case of patients with more severe disability, it is even more relevant to achieve a complete picture of the patients' conditions beyond her neurological status. Psychosocial and cognitive disturbances should be investigated and carefully evaluated in a multidisciplinary setting. In such cases the counseling about pregnancy should consider the presence and efficacy of family supportive network to sustain and help the mother.

Pregnancies do not always happen overnight. In your experience with your patients, how long does it take on average from the desire to get pregnant until confirmed pregnancy? Have you observed any factors that influence this time span?

Overall, fertility does not seem to be impaired to a larger extent in women with MS. However sexual symptoms could sometimes impact on the ability to conceive. As in western countries 10 to 20% of all couples suffer from infertility, we should consider that time to conception in MS patents is unpredictable as for healthy women. One of the great challenges in the management of the pre-pregnancy journey of our patient is to avoid exposing women to a prolonged washout period between the discontinuation of proper medications and the moment of conception that is in order to minimize the risk of relapse while waiting for a successful conception.

Large datasets providing solid information on the influence of available medications on fertility and maternal and foetal outcomes of exposed pregnancy are therefore of paramount importance for appropriate counseling.

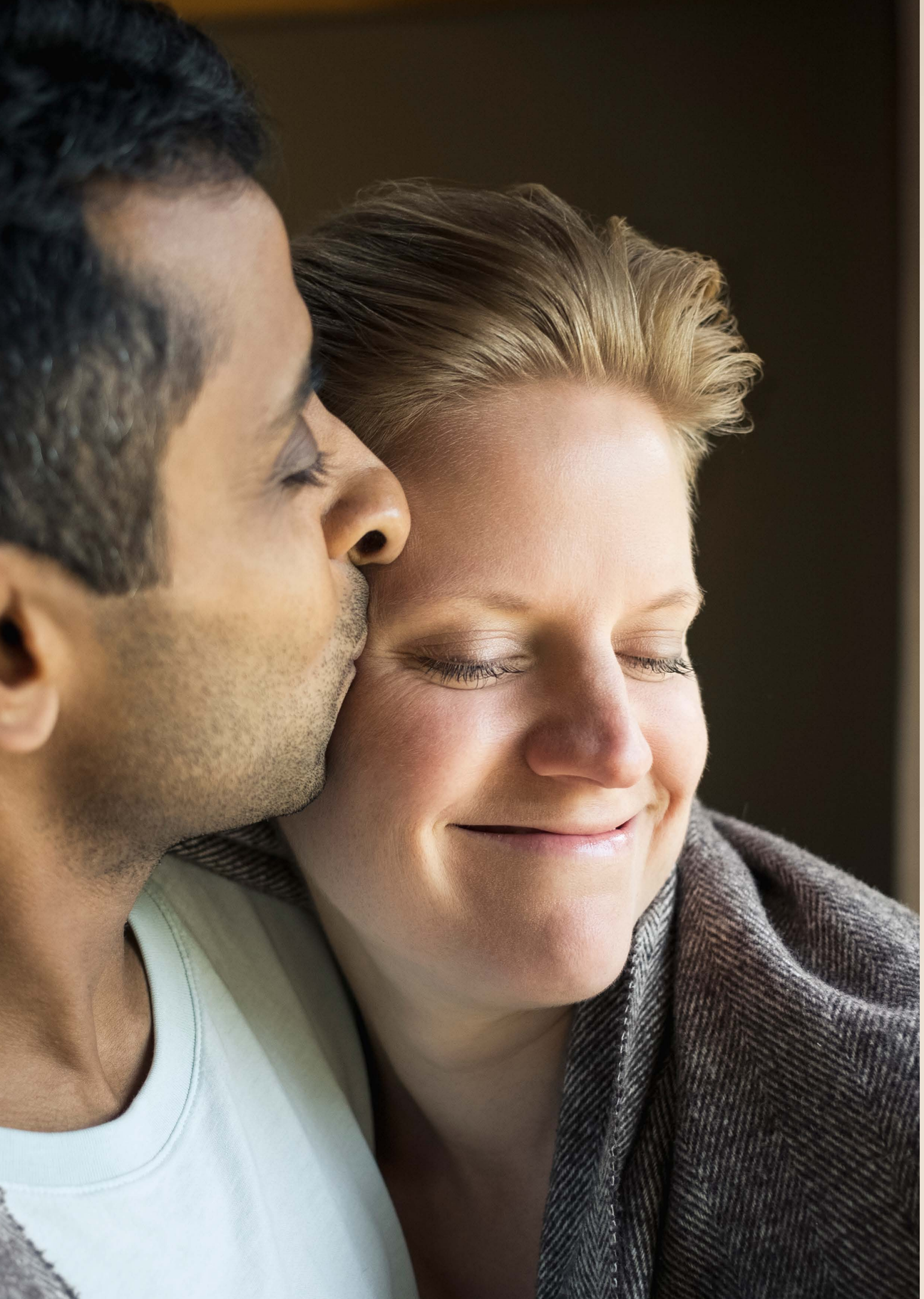
Our patients are usually encouraged to undergo a pre-pregnancy consultancy with the gynaecologist and when necessary with the immunologist of the team: many factors other than neurological considerations such as the management of autoimmune comorbidity with special focus on thyroid functioning, implementation of folic acid and vitamin D are taken into consideration.

In an ideal setting, patients with MS plan their pregnancies in advance. Do you see also unplanned pregnancies? If so, how many?

Up to 50% of pregnancies in women with MS are unplanned. For such a reason, all women with MS of reproductive age should be counseled to ensure adequate reproductive planning. The neurologist should promote a proactive family counseling since the first visit when MS diagnosis is communicated to the patient. This counseling should include contraception options. Counseling on the use of effective contraception is crucial to optimally plan motherhood and prevent unintentional pregnancies. Based on current evidence, most contraceptive methods appear to be safe for women with MS and neurologists in collaboration with gynaecologists should help patients to choose the most appropriate approach. For women with MS taking potentially teratogenic medications, highly effective methods that are long-acting (e.g. intrauterine devices, implants) might be the best option.

> **Up to 50% of pregnancies in women with MS are unplanned. For such a reason, all women with MS of reproductive age should be counseled to ensure adequate reproductive planning. The neurologist should promote a proactive family counseling since the first visit when MS diagnosis is communicated to the patient.**

The desire of motherhood should be proactively investigated at each following clinical encounter especially when a therapeutical shift is needed. One of the objective of our project is to improve counseling in order to increase the percentage of desired pregnancy: this is one of the process indicator we are monitoring.



In your opinion which are the most important advices to your MS patients regarding pregnancy?

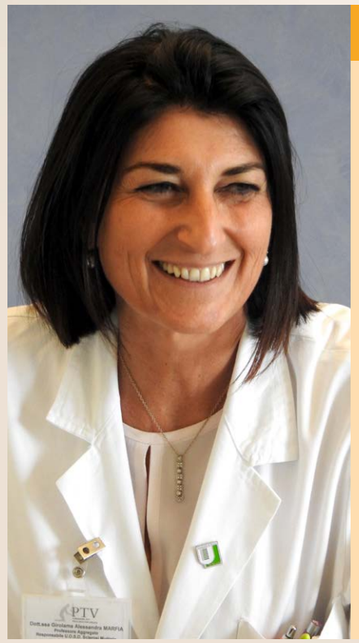
In my opinion, an important issue is that optimal planning and ideal monitoring start in the pre-pregnancy phase and involves several steps during pregnancy and postpartum, what we call the patient journey.

We need to stress that the type and course of the disease should be carefully evaluated when counseling a patient about pregnancy. Taken for granted that each decision should be shared with the patient, pregnancy plan should be delayed in the presence of highly active or aggressive disease as the immunomodulatory effect of gravidic hormones mainly expressed during the third trimester could be insufficient to suppress the disease inflammatory activity in these subgroups of patients.

In evaluating the type of MS at diagnosis We as clinicians should go beyond clinical and MRI presentation but we should take into consideration the course of the disease over time and in particular its response to the proposed therapy. In this optic, patients at the onset of the disease willing to have children in the short term should be counseled to postpone pregnancy plans to at least one year. A disease modifying treatment (DMT) compatible with conception should be the patient's first choice when possible.

> **Pregnancy in MS is a realistic option but it is of extreme relevance to be accompanied by your treating neurologist during each phase of this important journey.**

Clinicians are committed to inform MS patients that MS is not associated with adverse effects on pregnancy and the child's health and that the available evidence does not point to any major deleterious effect of pregnancy on the disease course. Pregnancy in MS is a realistic option but it is of extreme relevance to be accompanied by your treating neurologist during each phase of this important journey.



DR. GIROLAMA ALESSANDRA MARFIA

Dr. Girolama Alessandra Marfia is an Assistant Professor of Neurology in the Clinic of Neurology, System Medicine Department, University of Rome "Tor Vergata", Italy and is the Head of the Multiple Sclerosis Unit of the Tor Vergata University Hospital in Rome, Italy.

Her scientific interest and research concern the complex relationship between clinical, radiological, neurophysiological and CSF biomarkers of neuroinflammation and neurodegeneration in Multiple Sclerosis.
She is the Principal Investigator of many phase II, III and IV national and international trials with new therapeutic agents for Multiple Sclerosis conducted according to GCP. Dr. Marfia clinical and research interests extend also to acute and chronic inflammatory neuropathies and neuropathic pain.
A very important focus of Dr.Marfia is in the area of multiple sclerosis and pregnancy. In May 2016 she started the MS Pregnancy Unit, a special project focused on pregnancy in women with MS, in her MS Centre at Tor Vergata University Hospital in Rome. Dr. Marfia is author of about 80 peer-reviewed papers published in International Journals of Neuroscience and Neurology.

Betaferon®
(Refer to full SmPC before prescribing.)

Composition: *Active ingredient:* Recombinant interferon beta-1b 250 microgram (8.0 million IU) per ml when reconstituted. Betaferon contains 300 microgram (9.6 million IU) of recombinant interferon beta-1b per vial. *Excipients:* Human albumin, Mannitol. **Indications:** Betaferon is indicated for the treatment of patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite MS, patients with relapsing-remitting MS and two or more relapses within the last two years and patients with secondary progressive MS with active disease, evidenced by relapses. **Contraindications:** Patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin or any of the excipients. Patients with current severe depression and/or suicidal ideation. Patients with decompensated liver disease. **Special warnings / Precautions:** The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of systemic capillary leak syndrome with shock-like symptoms and fatal outcome. • In rare cases, pancreatitis was observed with Betaferon use, often associated with hypertriglyceridaemia. • Betaferon should be administered with caution to patients with previous or current depressive disorders, in particular to those with antecedents of suicidal ideation. Patients should be advised to immediately report symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with Betaferon and treated appropriately. Cessation of therapy with Betaferon should be considered. Betaferon should be administered with caution to patients with a history of seizures, particularly if their epilepsy is not adequately controlled with anti-epileptics. This product contains human albumin and hence carries the risk for transmission of viral diseases. A risk for transmission of Creutzfeld-Jacob disease cannot be excluded. • Thyroid function tests are recommended regularly in patients with a history of thyroid dysfunction or as clinically indicated. Complete blood and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. AST (SGOT), ALT (SGPT) and γ-GT), are recommended prior to initiation and at regular intervals during Betaferon therapy. Patients with anaemia, thrombocytopenia and/ or leukopenia may require more intensive monitoring. • Severe hepatic injury, including cases of hepatic failure, has been reported rarely in patients taking Betaferon. The most serious events often occurred in patients exposed to other drugs or substances associated with hepatotoxicity or with comorbidity. Patients should be monitored for signs of hepatic injury. Withdrawal of Betaferon should be considered if serum transaminases levels increase significantly or are associated with clinical symptoms. • Caution should be used and close monitoring considered with severe renal failure. • Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis, minimal change disease, membranoproliferative glomerulonephritis and membranous glomerulopathy have been reported, at various time points, during treatment with interferon-beta products and may occur after several years of treatment. Periodic monitoring of early symptoms and prompt treatment is required; and discontinuation of treatment with Betaferon should be considered, especially in patients at higher risk of renal disease. • Caution is required in patients with pre-existing cardiac disorders. Patients with pre-existing significant cardiac disease should be monitored for worsening of their cardiac condition, particularly during initiation of treatment with Betaferon. While Betaferon does not have known direct-acting cardiotoxicity, flu-like symptoms may prove stressful to pre-existing heart disease. Rare cases of cardiomyopathy have been reported: If this occurs and a relationship to Betaferon is suspected, treatment should be discontinued. • Cases of thrombotic microangiopathy (TMA), manifested as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome have been reported with interferon-beta products. Additionally, cases of haemolytic anaemia (HA) not associated with TMA, including immune HA, have been reported. Life-threatening and fatal cases have been reported. Cases of TMA and/or HA have been reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. If TMA and/or HA is diagnosed and a relationship to Betaferon is suspected, prompt treatment is required and immediate discontinuation of Betaferon is recommended.
• Serious hypersensitivity reactions may occur. If reactions are severe, Betaferon should be discontinued and appropriate medical intervention instituted. • Injection site necrosis has been reported in patients using Betaferon. It can be extensive and may result in scar formation. If the patient experiences any break in the skin, the patient should be advised to consult with his/her physician before continuing Betaferon injections. If the patient has multiple lesions Betaferon should be discontinued until healing. **Undesirable effects:** At the beginning of treatment adverse reactions are common but in general they subside with further treatment. The most frequently observed adverse reactions are a flu-like symptom complex and injection site reactions. Dose titration is recommended at the start of treatment in order to increase tolerability to Betaferon. Flu-like symptoms may be reduced by administration of non-steroidal anti-inflammatory drugs. The incidence of injection site reactions may be reduced by the use of an autoinjector. **Undesirable effects which were significantly associated with Betaferon treatment in clinical trials:** *Very common:* lymphocyte count decreased, absolute neutrophil count decreased, white blood cell count decreased, headache, abdominal pain, alanine aminotransferase increased, rash, hypertonia, myalgia, injection site reaction, flu-like symptoms, fever, asthenia, chills; *Common:* abnormal vision, palpitation, hypertension, dyspnoea, vomiting, aspartate aminotransferase increased, menstrual disorder, injection site necrosis, chest pain, sweating, malaise. **Undesirable effects identified during post-marketing surveillance:** *Very common:* arthralgia; *Common:* anaemia, hypothyroidism, blood bilirubin increased, weight increased, weight decreased, confusional state, tachycardia, urticaria, pruritus, alopecia, menorrhagia; *Uncommon:* thrombocytopenia, blood triglycerides increased, suicide attempt, emotional lability, convulsion, hepatitis, skin discolouration, nephrotic syndrome, glomerulosclerosis; *Rare:* thrombotic microangiopathy including thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome, anaphylactic reactions, hyperthyroidism, thyroid disorders, anorexia, cardiomyopathy, bronchospasm, pancreatitis, hepatic injury, hepatic failure. *Frequency not known:* haemolytic anaemia, capillary leak syndrome in pre-existing monoclonal gammopathy, drug-induced lupus erythematosus, pulmonary arterial hypertension.

Please refer to the Summary of Product Characteristics for further information.
On prescription only.
Marketing Authorisation Holder: Bayer AG, 51368 Leverkusen, Germany.
Date of issue of Marketing Authorisation valid throughout the EU: 30.11.1995.
Date of last Renewal: 31.1.2006. **Date of last SPC revision:** 29.10.2020

PP-BET-ALL-0187-1

BETAFERON®
Interferon beta-1b