

INTERNATIONAL CORNER

OBSTETRICS MONITORING IN ACROMEGALIC PATIENTS

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ABSTRACT

Acromegaly complicating pregnancy is rare. Glucose intolerance occurs in 50% of patients with acromegaly, sodium retention leads to hypertension in 25-35% of patients, with potential for exacerbation in pregnancy. Octreotide is a synthetic octapeptide of somatostatin, with plasma half-life of about 90 minutes, vs 2-6 minutes of somatostatin. We carried out a monitoring and a treatment with Octreotide of a 36-year-old woman, nulliparous, with active acromegaly despite double pituitary surgery. US imaging of fetal development has been performed, since the 10th till the 38th week. Eco-color-doppler has been used to examine the umbilical and uterine arteries at 16, 29, 33, 36 weeks, in agreement to octreotide infusion. The Doppler flow imaging has been made at beginning of headache, so that has been recorded placenta and uterine flow before and during and after octreotide infusion, till clearing up of headache. The comparison of uterine artery flussimetry show a statistical significant difference between the pre-OCT and post-OCT systolic velocity peak ($P < 0.0001$) and end diastolic velocity peak ($P < 0.0005$). The pregnancy was uneventful for both mother and fetus. Have been described the cases of women with acromegaly treated with octreotide during pregnancy. No malformations were noted but because of limited data, the use of somatostatin analogs cannot be recommended for use during pregnancy except under extraordinary circumstances.

Key words: *acromegaly; octreotide; pregnancy; color-power-doppler*

RIASSUNTO

Acromegaly complicating pregnancy is rare. Glucose intolerance occurs in 50% of patients with acromegaly, sodium retention leads to hypertension in 25-35% of patients, with potential for exacerbation in pregnancy. Octreotide is a synthetic octapeptide of somatostatin, with plasma half-life of about 90 minutes, vs 2-6 minutes of somatostatin. We carried out a monitoring and a treatment with Octreotide of a 36-year-old woman, nulliparous, with active acromegaly despite double pituitary surgery. US imaging of fetal development has been performed, since the 10th till the 38th week. Eco-color-doppler has been used to examine the umbilical and uterine arteries at 16, 29, 33, 36 weeks, in agreement to octreotide infusion. The Doppler flow imaging has been made at beginning of headache, so that has been recorded placenta and uterine flow before and during and after octreotide infusion, till clearing up of headache. The comparison of uterine artery flussimetry show a statistical significant difference between the pre-OCT and post-OCT systolic velocity peak ($P < 0.0001$) and end diastolic velocity peak ($P < 0.0005$). The pregnancy was uneventful for both mother and fetus. Have been described the cases of women with acromegaly treated with octreotide during pregnancy. No malformations were noted but because of limited data, the use of somatostatin analogs cannot be recommended for use during pregnancy except under extraordinary circumstances.

Parole chiave: *acromegalia; octreotide; gravidanza; color-power-doppler*

INTRODUCTION

Somatostatin is released from the hypothalamus and pituitary level to inhibit various hormones (GH, PRL, ACTH, TSH, FSH, LH), and also exercises control on angiogenesis. Its analogues, Octreotide and Lanre-

otide, inhibit the secretion of "growth-hormone" (GH) to 90% of patients with acromegaly and in patients with neuroendocrine tumors (carcinoid). Octreotide is a synthetic octapeptide of somatostatin, with plasma half-life of about 90 minutes, versus the 2-6 minutes of somatostatin.¹

In pregnancy the normal pituitary gland enlarges from 660mg in the non-pregnant state to 760mg by term. This is mainly due to an increase in the number and size of the lactotrophic cells. This increase in pituitary size does not result in visual field changes if a woman has a normal pituitary gland prior to the pregnancy. By serial MRI² showed an increase pituitary volume of about 136% overall and an increase in vertical and AP Ø of 2.6mm on average and the signal intensity was increased relative to that in the non-pregnant state, and this may lead to misinterpretation.

Dinc et al.³ have found on MRI that during pregnancy the volume of the gland shows the high percentage of increase compared to its length, height and width. The maximum height of the gland does not exceed 10mm during pregnancy but it may exceed 10mm during the three days immediately postpartum. Elster et al.⁴ have found that throughout pregnancy the pituitary gland height increases linearly by approximately 0.08mm per week, but no gland exceeded 10mm in height during pregnancy. Increases in gland convexity also correlated with progression of pregnancy. The largest glands were seen in the immediate postpartum period and during this period 5 of 12 glands measured 10.0 to 11.8mm. Beyond the first week postpartum the pituitary gland size rapidly returned to normal, which was regardless of the status of breast feeding. The main diameter of the infundibulum was 2.2mm. The normal physiologic changes in pituitary hormone concentrations in pregnancy mean that it is very difficult to diagnose pituitary hyper-secretion or hypo-secretion during pregnancy and postpartum period. The results of dynamic pituitary function testing in pregnancy are very difficult to interpret, as no standard exists^{5,6}.

Acromegaly complicating pregnancy is rare, the prevalence being 5/100,000 persons.⁷ Pregnancies in patients with acromegaly are uncommon, because 85% of these women have disturbances of ovulation primarily associated with hyperprolactinemia and impaired gonadotropin secretion. Excess growth hormone may also result in maternal diabetes, hypertension and left ventricular hypertrophy. Before pregnancy, active acromegaly should be treated by surgery, neoadjuvant radiotherapy or medical therapy if complete surgical ablation is not possible.

Long-acting somatostatin analogues are the medical treatment of choice in acromegaly and successful pregnancies after treatment with the analogue Octreotide have been reported.⁸

Conventional RIA-assays for GH cannot distinguish between normal pituitary GH and the placental GH variant. Therefore, these assays may yield misleading results, especially in the latter half of pregnancy when basal levels of the variant are considerably higher than normal non-pregnant growth hormone levels:⁹ pituitary GH in acromegaly is highly pulsatile, whereas secretion of the pregnancy GH variant is non-pulsatile; placental GH also does not respond to TRH.

The fetal-placental unit alters the maternal endocrine metabolism and hormonal feedback mechanisms and may be difficult to distinguish from the normal hypermetabolic state of pregnancy.

Data on the use of Octreotide during pregnancy is limited. Only 3 patients treated with Octreotide during pregnancy have been reported and no malformations were found in the children. Because of such limited data, some authorities recommend that Octreotide therapy be discontinued if pregnancy is considered and contraception should be used when Octreotide is administered.¹⁰

The pregnancy has exacerbated the underlying condition in 4 of the 24 (17%) pregnant patients with acromegaly who have been described in the literature.¹¹ Tumor enlargement during pregnancy has been described in 2 patients with acromegaly.¹²

Glucose tolerance, hypertension, and cardiac derangements also require monitoring. Glucose intolerance occurs in 50% of patients with acromegaly, with overt diabetes mellitus in 10-20%.¹³ The risk for gestational diabetes mellitus is consequently increased by the insulin resistance of acromegaly. Sodium retention leads to hypertension in 25-35% of patients, with potential for exacerbation in pregnancy. Because of their underlying cardiomyopathy and increased risk for coronary artery disease, these complications may also be exacerbated during pregnancy.¹⁴ GH does not cross the placenta, and maternal acromegaly has little direct impact on the fetus. Fetal somatic growth is largely GH-independent, and macrosomia in such pregnancies is likely secondary to maternal glucose intolerance.

Somatostatin analogs can cross the placenta. Ten cases of women with acromegaly treated with octreotide during pregnancy have been described,¹⁵ two cases with acromegaly treated with lanreotide,^{16,17} one with a TSH-secreting tumor treated with octreotide during pregnancy,¹⁸ and one with nesidioblastosis treated with octreotide during pregnancy.²⁰ In most cases the somatostatin analog was stopped before the end of the

first trimester, but in two cases octreotide was given throughout the pregnancy.¹⁹ No malformations were noted in any case, but because of such limited data, the use of somatostatin analogs cannot be recommended for use during pregnancy except under extraordinary circumstances.⁵

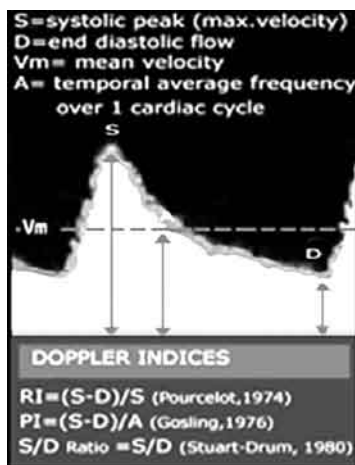
However, clinical experience with SSA treatment during pregnancy is still limited and SSAs are usually discontinued early in gestation if pregnancy occurs or at the time of pregnancy planning.^{11,20}

Somatostatin analogues can cross the placenta and reach both the foetal circulation and the foeto-maternal biological fluids^{15,18,19} and in some cases, foetal growth retardation was observed.¹⁵

Routine monitoring of fetal growth and welfare is done by studying flow by echo-color-Doppler fetal and maternal vessels.

The uterine artery is evaluated by measuring the blood flow velocity at peak systole (maximal contraction of the heart) and peak end diastole (maximal relaxation of the heart). The most common approach is to measure the Doppler Velocimetry Indices (**Fig.1**).

Figure 1: Doppler velocity indices (PI = pulsatility index; RI: resistance index; S/D = systolic peak/end diastolic flow).



In non-pregnant uterine artery (UA) with a high resistance to blood flow, the waveform demonstrates notching (B) at the beginning of diastole with low flow at the end of diastole (C) (**Fig.2**). In pregnant uterine artery, as the result of dilation of vessels in the placenta, blood flow increases during diastole. In early pregnancy the peak flow at diastole is less than later in pregnancy. Therefore, as the duration of pregnancy increases, the amount of blood flowing in the uterine artery increases during diastole. (**Fig.3**) If the resistance to flow increase to a value above the upper range of normal, this identifies a fetus at risk or who has IUGR.

The mild notching of the UA is a more serious waveform because there is a “notch” at the beginning of di-

Figure 2: Doppler Velocimetry in non-pregnant uterine artery.

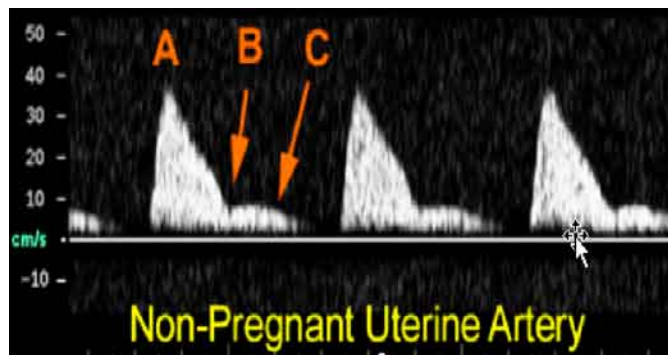
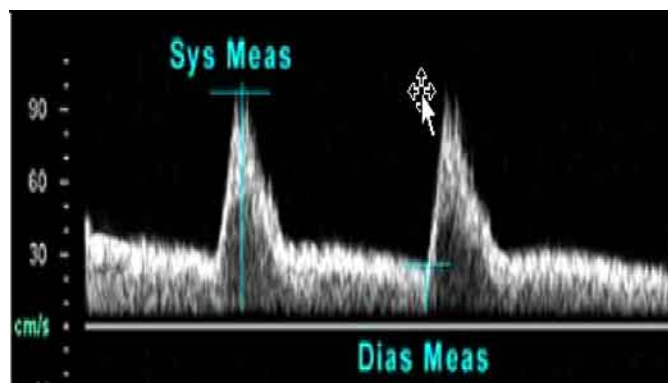
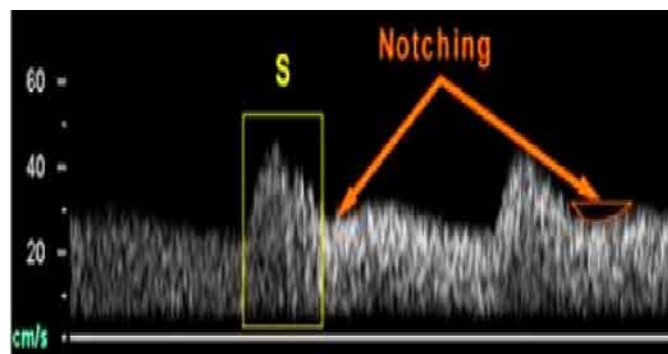


Figure 3: Doppler Velocimetry in pregnant uterine artery.



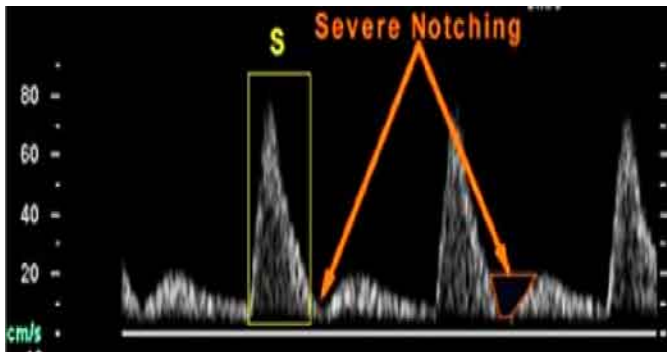
astole. The notch is the result of an increase in resistance to blood flowing into the placenta, because the blood vessels in the placenta are not enlarging or dilating as they should. However, as in **Fig.4**, blood flow at the end of diastole appears to be normal.

Figure 4: Doppler Velocimetry: the mild notching of the UA.



The presence of a notch, even with a normal resistance to flow, places the patient at high-risk for adverse fetal outcome. In the severe notching (**Fig.5**) with an abnormal resistance index, the patient is at the highest risk for adverse pregnancy outcome. Recent studies have found that surveillance of high-risk fetuses with

Figura 5: Doppler Velocimetry: the severe notching with an abnormal resistance index.



abnormal uterine blood flow may decrease morbidity and mortality. Development of the uteroplacental circulation is crucial for a normal pregnancy outcome, because the normal uterine blood flow at term was estimated at 500-700 ml/min with a two- to three-fold decrease in uteroplacental perfusion noted in the presence of preeclampsia (PE).

The abnormal uterine artery Doppler waveforms were associated with more proteinuric hypertension, required more antihypertensive therapy and resulted in lower birth weights and younger gestational ages at birth. Defective placentation due to failing trophoblast invasion occurs in the first half of pregnancy and this might result in early and severe clinical manifestations of PE. In contrast, maternal factors, such as diabetes, essential hypertension or coagulation disorders, might cause PE by inducing changes in normally developed uteroplacental arteries.

There is evidence that increased impedance to flow in the UA is associated with increased risk for subsequent PE development, IUGR and perinatal death.^{21,22} In addition, women with normal impedance to flow in the UA constitute a group that have a low risk of developing obstetric complications related to uteroplacental insufficiency, Doppler assessment of uterine arteries is an accurate tool to assess uteroplacental resistance to blood flow and, therefore, is a good method to investigate insufficient or lacking dilatation of the spiral arteries: in uncomplicated pregnancies, the spiral arteries undergo a series of changes that convert them from small-diameter, high-resistance vessels into low-resistance nonresponsive channels.²³

In these cases, the uteroplacental circulation remains in a state of high resistance, which causes generalised endothelial cell injury. Activated or injured endothelial cells lose their ability to maintain vascular integrity,

which leads to an increase in capillary permeability, platelet thrombosis and increased vascular tone.

The impedance to flow in the uterine arteries decreases with gestation in normal pregnancies, reflecting the trophoblastic invasion of the spiral arteries and their conversion into low-resistance vessels.²⁴

METHODS

We carried out a monitoring and a treatment with Octreotide of a 36-year-old, parity 0000, woman with active acromegaly despite double pituitary surgery. A written informed consent was obtained before. She took the following medications: L-tiroxine; fenobarbital; aspirin; iron and folic acid supply; OCT 0.1 mg s.c. every 1-2 h (120-240 mg daily) for headache relieving.

We monitored the patient since the beginning through the following parameters: hormonal values of the mother (GH; IGF-I; FT3; FT4; TSH); OCT levels of biological fluids (serum mother; umbilical cord serum; amniotic liquid; serum child; colostrum); coagulation, epato-renal, virological, microbiological, genetic tests, oral glucose tolerance tests, Holter pressure test and echocardiography.

US imaging of fetal development has been performed, since the 10th till the 38th week, through the biometry of the head (BPD, CC), abdomen (AC) and upper-lower limbs (FM, OM). The morphological fetal evaluation and the echotomography of liver, kidney, pancreas, gallbladder of the mother has been performed at each control (10, 16, 29, 33 and 36 wks of gestation), and colour flow mapping of umbilical, fetal and uterine vessels, either transabdominally (at the UA crossover with the external iliac artery) or transvaginally (at the UA lateral to the uterine cervix at the level of the internal cervical canal).

The proximal part of the uterine artery, where it crosses the external iliac artery, proved easy to identify and adequate signals could be recorded in all cases. the uterine arteries reflect the total resistance to blood flow in the distal uteroplacental vasculature, whereas these smaller arteries (arcuate or radial arteries) do not. The process of physiological adaptation of the spiral arteries is usually completed at the 22nd week of pregnancy and, therefore, Doppler assessment of the uterine arteries, before and after this period, is a useful tool to determine whether placentation has developed normally.

All US sophisticated controls has been performed by

the same obstetric specialized and expert in ultrasound techniques, using an Siemens Elegra equipped with color-power-doppler, 3.5 and 5.0 MHz convex abdominal probe, 6.5 MHz endovaginal probe and special software for haemodynamic calculations in real time for all blood flow measurements before and after OCT 0.1 mg s.c. (given at request for headache) at 10, 16, 29, 33 and 36 wks of gestation; child's hormones and anthropometry after delivery was performed. Statistical analysis was performed by using the analysis of variance when comparisons were made between more than two groups and the data were normally distributed. If statistical significance was shown, the Scheffé F-test was used for further analysis. If the data were not normally distributed, the nonparametric Kruskal-Wallis test was chosen. Between two groups, comparisons were made by using Student t-test if the data were normally distributed. Otherwise, the Mann Whitney U-test was chosen. Linear regression analysis was used to show the relationship between umbilical vein and artery. The categorical data were compared using the chi-square test. A p value of 0.05 or less was selected as the level of statistical significance.

RESULTS

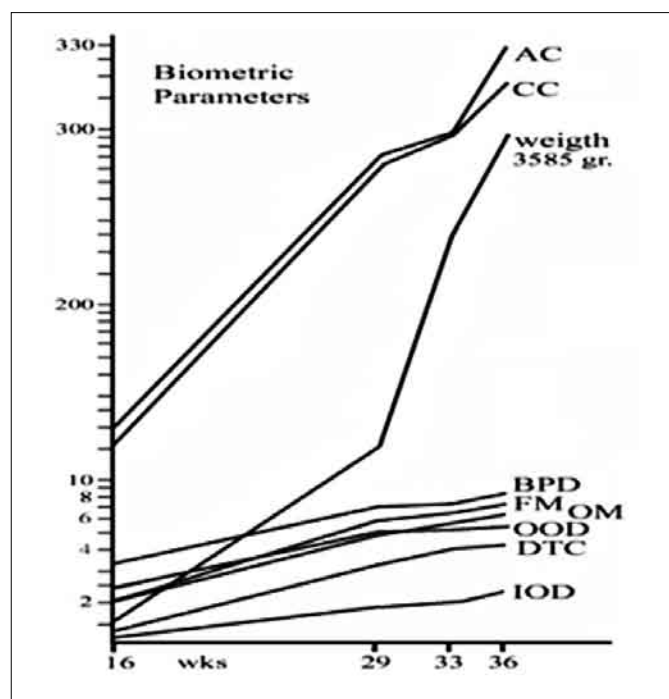
The pregnancy was uneventful for both mother and fetus. The infant was delivered at 9th months of gestation by an elective cesarian section. At birth and follow-up (1 yr) the infant was normal.

The fetus growth has been regular (50° percentil), corresponding amount of amniotic fluid was always observed related to gestational week and placenta morphology an agreement with the different ages of gestation; at 33 weeks has been suspected a clubfoot, not confirmed at birth.

US imaging of fetal development has been performed, since the 10th till the 38th week, through the biometric parameters of the head (BPD, CC), abdomen (AC) and upper-lower limbs (FM, OM,), as showed in **Fig.6**. The single parameters and cephalic-abdominal-periferic ratio was observed as normally, during pregnancy and at birth, like to the fetal weight.

Eco-color-power-doppler has been used to examine the umbilical and the uterine arteries at 16, 29, 33, 36 weeks, in agreement to octreotide infusion. The Doppler flow imaging has been made at beginning of headache, so that has been recorded placenta and uterine flow before and during and after octreotide infusion, till clearing up of headache.

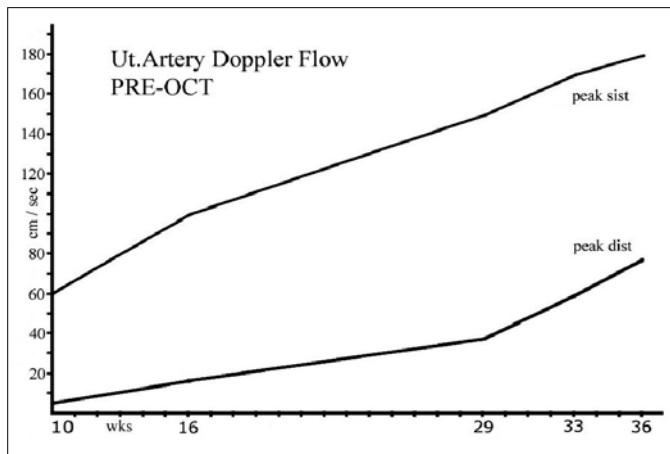
Figure 6: US imaging of fetal development since the 10th till the 38th week.



During infusion has not been noticed significant changes in fetus motion neither in fetus breathing movements, neither has been reported significant changes of fetus heart frequency and changes of heart and brain flow. Reached fetus neurological maturity, has been planned an elective cesarian section at 38 weeks. The newborn was female and weighted 3585 gr./ 49 cm. The Apgar score was 8/10 - 10/10 and the placenta's histological exam didn't show significant modification octreotide-correlated. Octreotide plasma concentrations measured in umbilical cord blood directly after birth clearly indicated significant materno-fetal transfer of octreotide.

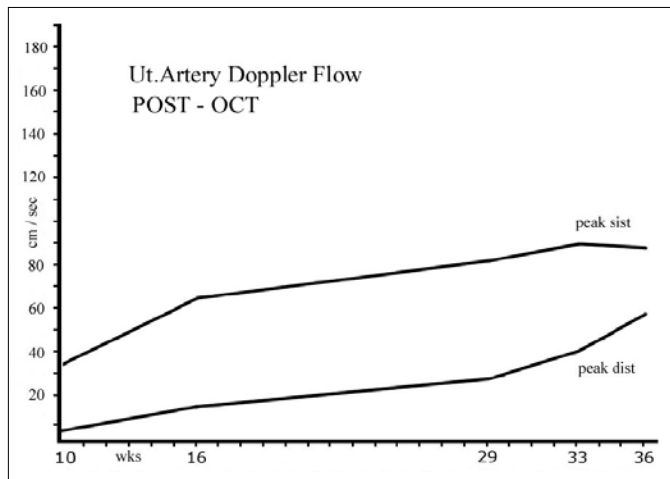
The velocities peaks plotted in **Fig.7**, show the systolic and diastolic values of the uterine artery of the patient during pregnancy, with evidence of normal growing blood flow at the uterus. The peak systolic ranged (from 10 to 36 wks) between 60.5 and 179 cm/s with a 33.8% of velocity flow growth, while the peak end diastolic ranged between 5.2 and 78.2 cm/s with a 6.6% of velocity flow growth. Despite the octreotide plasmatic half-life was about 90 min, we observed a strong changing of uterine blood flow within 5 min, with prompt disappearance of headache and comebacke at previously uterine flow condition within 10 min, with persistence of maternal wellbeing drug-induced. The uterine artery velocities observed within 5 min from

Figure 7: The velocities peaks systolic and diastolic of the uterine artery of the patient during pregnancy, with evidence of normal growing blood flow at the uterus.



drug infusion show (Fig.8) a systolic range from 33.1

Figure 8: The uterine artery velocities observed within 5 min from drug infusion.

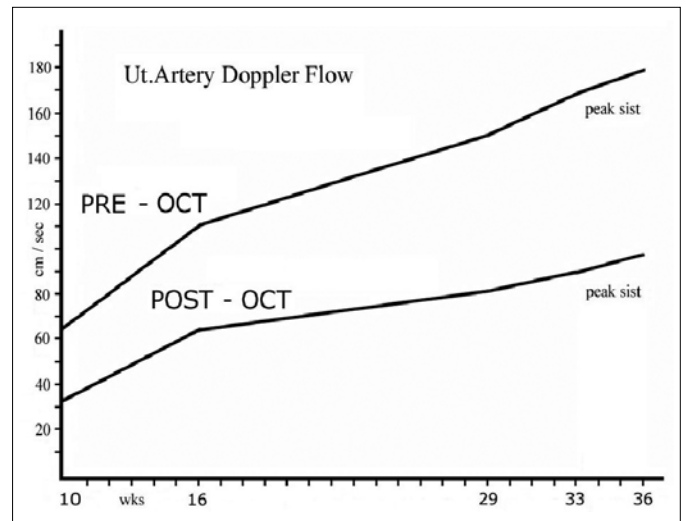


to 88.1 cm/s with a 37.6% of velocity flow growth, while an end diastolic range from 5.6 and 58.1 cm/s with a 8.6% of velocity flow growth.

The strong flow decrease in the uterine artery find explanation on vasodilatation of splanchnic vessels, without penalization of Doppler velocimeters indices (PI, RI, S/D). I mean, the Doppler indices make known condition of flow resistance, but if there is a dilatation of all vessel tree, obviously the velocity change but not the resistance index.

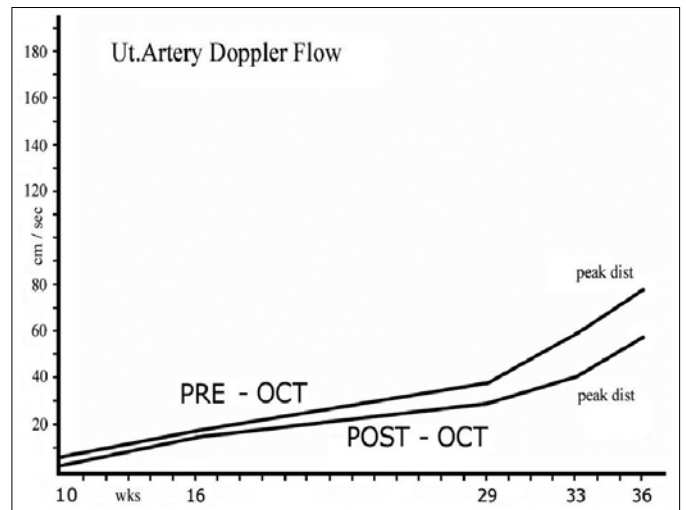
The comparison of uterine artery flussimetry in the pre-post infusion show a statistical significant difference between the pre-OCT and post-OCT systolic velocity peak ($P < 0.0001$) (Fig.9), and

Figure 9: The comparison of systolic uterine artery flussimetry in the pre and post drug infusion.



end diastolic velocity peak ($P < 0.0005$) (Fig.10), in each step studied.

Figure 10: The comparison of diastolic uterine artery flussimetry in the pre and post drug infusion.

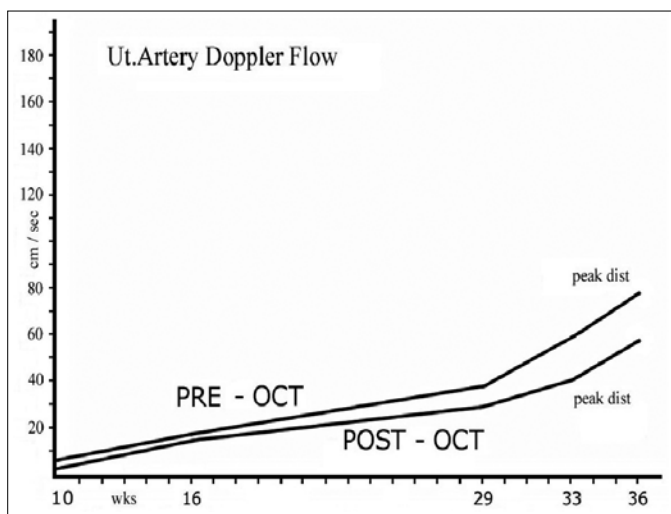


Since it is normal to observe a progressive reduction of PI, RI and S/D value during pregnancy, the variations of these indices in pre/post infusion has been less sensible ($P < 0.009$), as well showing a progressive reduction from 10 to 36 wks and confirming that the OCT infusion don't produce negative effects on uterine circulation during pregnancy.

The PI reduction pre-post OCT was -19.9% (range: -8.7 to -39.26) ($P < 0.009$); the RI reduction was -17.4% (range: -8.7 to 40.4) ($P < 0.009$); the S/D reduction was -34.12% (range: -23 to -49.4) ($P < 0.0006$).

The better S/D index data was plotted (**Fig.11**) in order to realize the meaning.

Figura 11: Comparison S/D pre and post drug somministrazione.



The S/D is a fraction in which the value of the numerator and the denominator explain the phenomenon, regarding to the increase in uterine artery blood flow during normal pregnancy: from 50 ml/min (0.83 ml/sec) in early pregnancy to 700 ml/min (11.66 ml/sec) at term

The mean velocity peak systolic of all check was 135.2 cm/s (pre-OCT) and 71.58 cm/s (post-OCT) with a velocity reduction of -47%, while the mean velocity end peak diastolic of all check was 39.54 cm/s (pre-OCT) and 29.6 cm/s (post-OCT), with a velocity reduction of -25%. I mean, the reduction of the velocity peak systolic (numerator) was 2 time more than velocity peak diastolic (denominator).

DISCUSSION

Many differences in Doppler technique employed in the different studies that showed different definition of abnormal flow cut-off in ultrasound velocimetry and the gestational age for the diagnosis of preeclampsia and intrauterine growth retard.

We investigated three more sensitive aspects of the octreotide treatment in pregnant woman. The first important aspect is the screening for pre-eclampsia (PE): An important finding of the studies is that uterine artery Doppler is better at predicting severe rather than mild disease. Steel et al.²⁵ show that the sensitivity

of increased impedance in the uterine arteries for PE was 63% and for gestational hypertension it was 39%, while for Papageorghiou et al.²⁶ the sensitivity for PE with IUGR was 69%, and for PE without IUGR it was 24%. About the gestation age, Harrington et al.²⁷ found that bilateral notching at 24 wks identified 55% of women who later developed PE, and this rose to 81% for PE requiring delivery before 35 wks. Albaiges et al.²⁸ showed that the sensitivity of increased PI or bilateral notches in predicting PE was 45% whereas for PE requiring delivery before 34 weeks the sensitivity was 90%. Papageorghiou et al.²⁶ reported that increased PI identified 41% of women who later developed PE; the sensitivities for PE requiring delivery before 36, 34 and 32 weeks were 70, 81 and 90%, respectively.

The second important aspect is the screening for intrauterine growth retard (IUGR). In women with increased impedance to flow in the uterine arteries, the pooled probability for the delivery of a IUGR was about 3.7; it was 0.8 for those with normal Doppler results. As for the prediction of PE, the studies agreed that the sensitivity of abnormal Doppler results was higher in more severe degrees of IUGR. Thus, in studies providing data on birth weight below the 10th, 5th and 3rd centiles, an increase in sensitivity was seen with decreasing birth weight centile. The improved sensitivity in the prediction of severe disease is also demonstrated by studies examining IUGR with preterm delivery. Harrington et al.²⁷ found that bilateral notching at 24 wks identified 22% of women who later delivered infants with birth weight below the 10th centile and the sensitivity improved to 58% for growth restriction requiring delivery before 35 wks. Albaiges et al.²⁸ reported that mean PI above the 95th centile of the normal range at 23 wks identified 21% of pregnancies delivering an IUGR with weight < 10th centile and 70% for weight < 10th centile delivering before 34 wks. Papageorghiou et al.²⁶ reported that mean PI above the 95th centile of the normal range at 23 wks identified 16% of pregnancies delivering an IUGR with weight < 10th centile and that this increased to 53, 64 and 74% for weight < 10th centile delivering before 36, 34 and 32 weeks, respectively. Most 1st trimester screening studies have shown that the impedance to flow in the uterine arteries is increased in pregnancies that subsequently develop PE and IUGR. In women with increased impedance to flow, the probability for the development of PE was about 5 and for those with normal Doppler results

about 0.5; the probability for IUGR were about 2 and 0.9, respectively.

In the 2nd trimester screening, the prediction of PE and IUGR was higher for these complications requiring preterm delivery. Thus, in the study of Martin et al.²⁹, the sensitivities for PE requiring delivery before 36, 34 and 32 wks were 40, 50 and 60%, respectively, and for IUGR they were 22, 24 and 28%, respectively. The sensitivities were found to be lower in 1st vs 2nd trimester screening, and the authors concluded that the potential advantage of earlier identification of a high-risk group might make prophylactic interventions more effective.²⁹

The third aspect is the screening for fetal/perinatal death by Doppler screening: The large differences in the Doppler sensitivity (8–83%), could reflect the small number of cases in each study. Steel et al.²⁵ reported 27 fetal deaths (1.5%) whose a sensitivity and specificity of an abnormal Doppler were 19 and 84%, respectively. In the pooled data the probability for subsequent fetal or perinatal death in women with increased impedance to flow was 2.4, whereas for those with normal Doppler results it was 0.8.²⁴

The major arterial blood supply to the uterus is derived from the uterine arteries and blood velocity waveform indices in the uterine artery remain high and quite stable during the first trimester of pregnancy³⁰. In the beginning of the second trimester, Doppler indices decrease sharply and early diastolic notching of uterine artery disappears. However, a diastolic notch can be a normal finding until 26 weeks of gestation.³¹ The Doppler indices of the uterine artery on the placental side are significantly lower than on the nonplacental side and a centrally located placenta demonstrates similar Doppler indices on both sides.³² Abnormal uterine artery blood velocity waveforms are identified by a persistent abnormal index, a persistent diastolic notch or an abnormal difference between the indices in the left and right uterine arteries^{33,34} and abnormal umbilical artery blood velocity waveforms in humans are associated with a decrease in the number of small muscular arteries in the placental tertiary stem villi.^{35,36} These morphologic changes may deteriorate the placental oxygen and other nutritional transport, and lead to IUGR. The maternal blood supply to the placenta is intermittently reduced by miometrial contractions (intrauterine pressure > 30 mmHg) through an increase of vascular flow resistance in uterine ar-

teries (intrauterine pressure > 35 mmHg) and, end-diastolic disappears.³⁷

At contrary, the umbilical artery blood flow is not affected by uterine contractions. Moreover, the flow velocity waveforms differs in different parts of UA during contractions: in the UA ascending branches is present in whole heart cycle, whereas in the UA descending branches, (supplying the uterine cervix and the upper vagina) the reversed diastolic flow appears.³⁸ The flow velocity reduction and the UA pulsatility index (PI) are related to intrauterine pressure and the UA reversal flow may appear during uterine inertia.³⁹ In the low-risk population the screening efficacy of uterine artery Doppler was disappointing but is generally in agreement with studies in populations with a low prevalence of PE and IUGR.^{40,41,42} The results of this study confirm the potential of uterine artery Doppler in the screening of high-risk population for uteroplacental complications during pregnancy. High-risk women with normal uterine artery waveforms have a similar risk of developing antenatal complications related to abnormal placentation as do women with uncomplicated obstetric history. In this study, with OCT-therapy in pregnancy, it was expected a maternal cause of obstetrical pathology, so a longitudinal umbilical and uterine vessels blood flow monitoring has been the best procedure to pick fetus out, immediately, with abnormal growth, because the octreotide reduce blood levels as potent inhibitor of GH, insulin, and glucagon secretion and also decreases splanchnic blood flow and inhibits release of serotonin, gastrin, vasoactive intestinal peptide. The fetal intensive care demonstrated a progressive fetal well-being both during OCT-infusion period, and as regards global growth.

At best of our knowledge only six other patients have been treated with somatostatin analogues throughout all pregnancy: 4 with GH-secreting tumors (3 OCT; 1 OCT-LAR); 1 with TSH secreting tumor (OCT-LAR), and 1 with nesidioblastosis (OCT). A few other patients have been exposed to OCT for a limited time during gestation and despite the transplacental passage it does not seem to affect fetus development. However, OCT deeply influence normal subjects' splanchnic circulation and it has been able to cause both a decrease of portal vein and superior mesenteric artery blood flow. Although splanchnic blood is conveyed to placenta and fetus by means of uterine artery, thus influencing their growth, there are any data on OCT effects on uterine artery flow.^{15, 43,44,45,46}

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