12° Congresso Nazionale AME
6th Joint Meeting with AACE

Bari,
7-10 novembre 2013

Focus on:
PROLATTINOMA E GRAVIDANZA

INDUZIONE DELLA GRAVIDANZA

Maurizio Poggi
Azienda Ospedaliera Sant'Andrea - Roma

Programma

Bari,
7-10 novembre 2013

- ✓Contestualizzazione
- ✓La giusta comunicazione
- ✓Quali quesiti / quali risposte
  - ➢Per la mamma
  - ➢Per il bambino
- ✓ Conclusioni

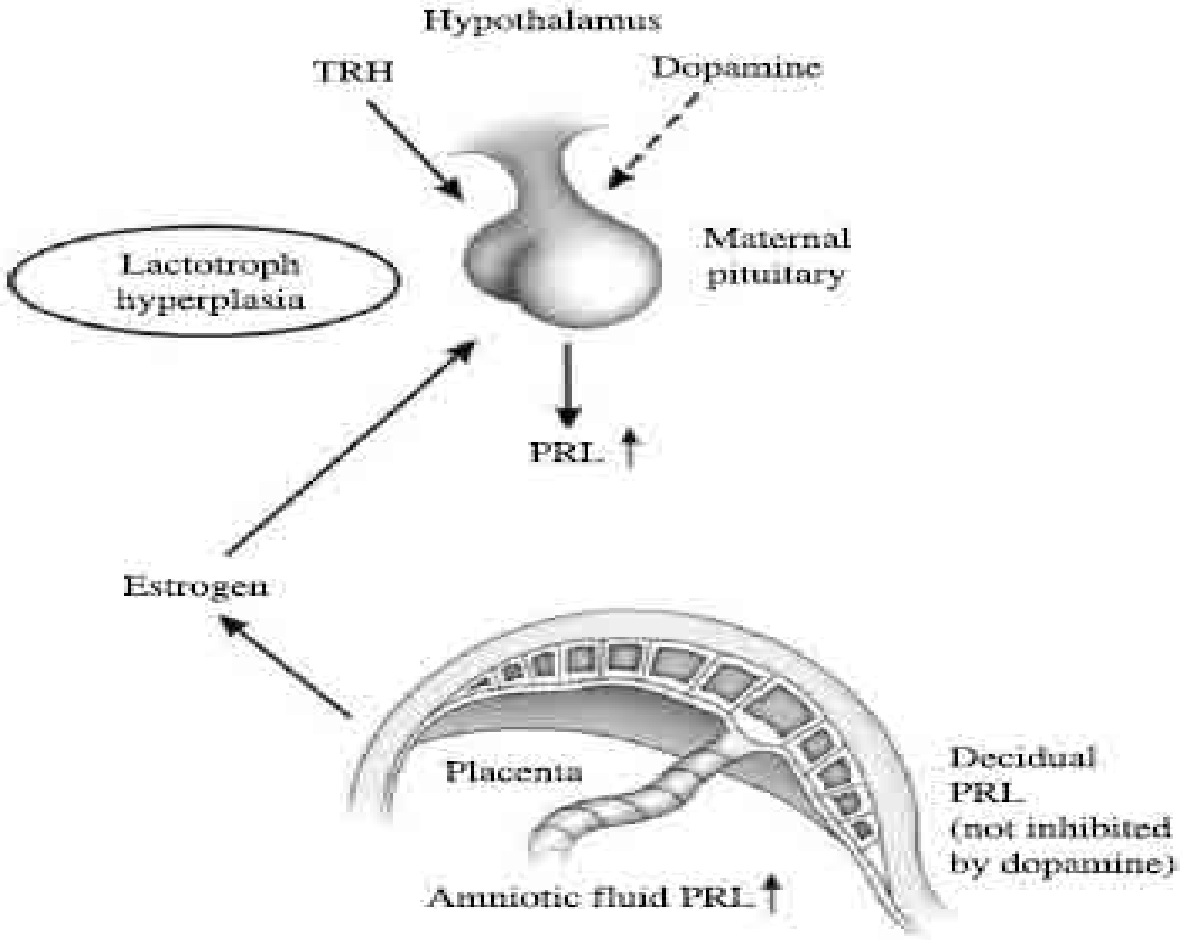


Figure 3 PRL axis during pregnancy: maternal PRL is increased during pregnancy due to estrogen-stimulated lactotroph hyperplasia with small contributions from decidual PRL. Maternal decidua is responsible for increased PRL in amniotic fluid. Unlike pituitary PRL, decidual PRL is not affected by TRH and dopamine.

Medical treatment of prolactinomas

Annamaria Colao and Silvia Savastano

NATURE REVIEWS | ENDOCRINOLOGY VOLUME 7 | MAY 2011

Introduction

Prolactin-secreting adenomas are the most predominant type of all pituitary tumors. The estimated prevalence is 100 prolactinomas per million adults,[1] although Ciccarelli *et al.*[2] reported an even higher prevalence of 775 per million adults in Belgium. The incidence of prolactinomas varies with age and sex; these tumors occur with the highest frequency in women aged 20–50 years, at which point the ratio between the sexes is estimated to be 10:1. In adults aged >60 years, prolactinomas occur with a similar frequency in both sexes.[3,4] During childhood, pituitary tumors are rare; however, prolactinomas constitute about 50% of all pituitary adenomas in this subpopulation.[5]

Programma

Bari,
7-10 novembre 2013

- ✓Contestualizzazione
- ✓La giusta comunicazione
- ✓Quali quesiti / quali risposte
  - ➢Per la mamma
  - ➢Per il bambino

Bari,
7-10 novembre 2013

Prolactinomas and pregnancy

Prolactinomas are the most common cause of persistent hyperprolactinemia and account for 50% of the functioning pituitary tumors (134). After the use of bromocriptine as the first-line treatment in prolactinomas since the 1970s, pregnancies in patients lacking a previous history of surgery and growth of prolactinoma during gestation have been described. Women with prolactinomas who are on dopamine agonist therapy should be warned about the rapid restoration of fertility, sometimes before resuming the first menses. So when a

NECESSITÀ (UTILITÀ) DI PROGRAMMAZIONE

Programma

Bari,
7-10 novembre 2013

- ✓Contestualizzazione
- ✓La giusta comunicazione
- ✓Quali quesiti / quali risposte
  - ➢Per la mamma
  - ➢Per il bambino

Netherlands The Journal of Medicine MARCH 2010, VOL. 68, NO 3

REVIEW

Update in prolactinomas

M. Kars[1,2*], O.M. Dekkers[3,4], A.M. Pereira[3], J.A. Romijn[3]

Pregnancy

Two major issues arise in the treatment of prolactinomas and pregnancy: 1) effect of pregnancy on prolactinomas, and the possibility of growth of prolactinomas; 2) effect of dopamine agonists on foetal development.

with pituitary adenomas.[81-90] In women treated for microprolactinomas, quality of life is impaired, especially due to increased anxiety and depression.[91-92]

0163-769X/06/$20.00/0
Printed in U.S.A.

Endocrine Reviews 27(5):485–534

doi: 10.1210/er.2005-9998

Advances in the Treatment of Prolactinomas

Mary P. Gillam, Mark E. Molitch, Gaetano Lombardi, and Annamaria Colao

Division of Endocrinology, Metabolism, and Molecular Medicine (M.P.G., M.E.M.), Northwestern University Feinberg School of Medicine, Chicago, Illinois 60611; and Department of Molecular and Clinical Endocrinology and Oncology (G.L., A.C.), University "Federico II" of Naples, Naples 80131, Italy

IX. Pregnancy

The management of prolactinomas in pregnant women can be complex. Three major issues arise in the treatment of prolactinomas in pregnancy: 1) the effect of the pregnancy on the prolactinoma; 2) the effects of the dopamine agonist on early fetal development occurring before a pregnancy is diagnosed; and 3) the safety and efficacy of dopamine agonists after reintroduction for symptomatic tumor growth.

TABLE 10. Effect of pregnancy on prolactinomas

	Total no. of patients	Symptomatic enlargement	% Symptomatic enlargement	No. requiring surgery (%)
Microadenomas	457	12	2.6	
Macroadenomas	142	45	31	12 (8.5%)
Macroadenomas, prior surgery or radiation	140	7	5	

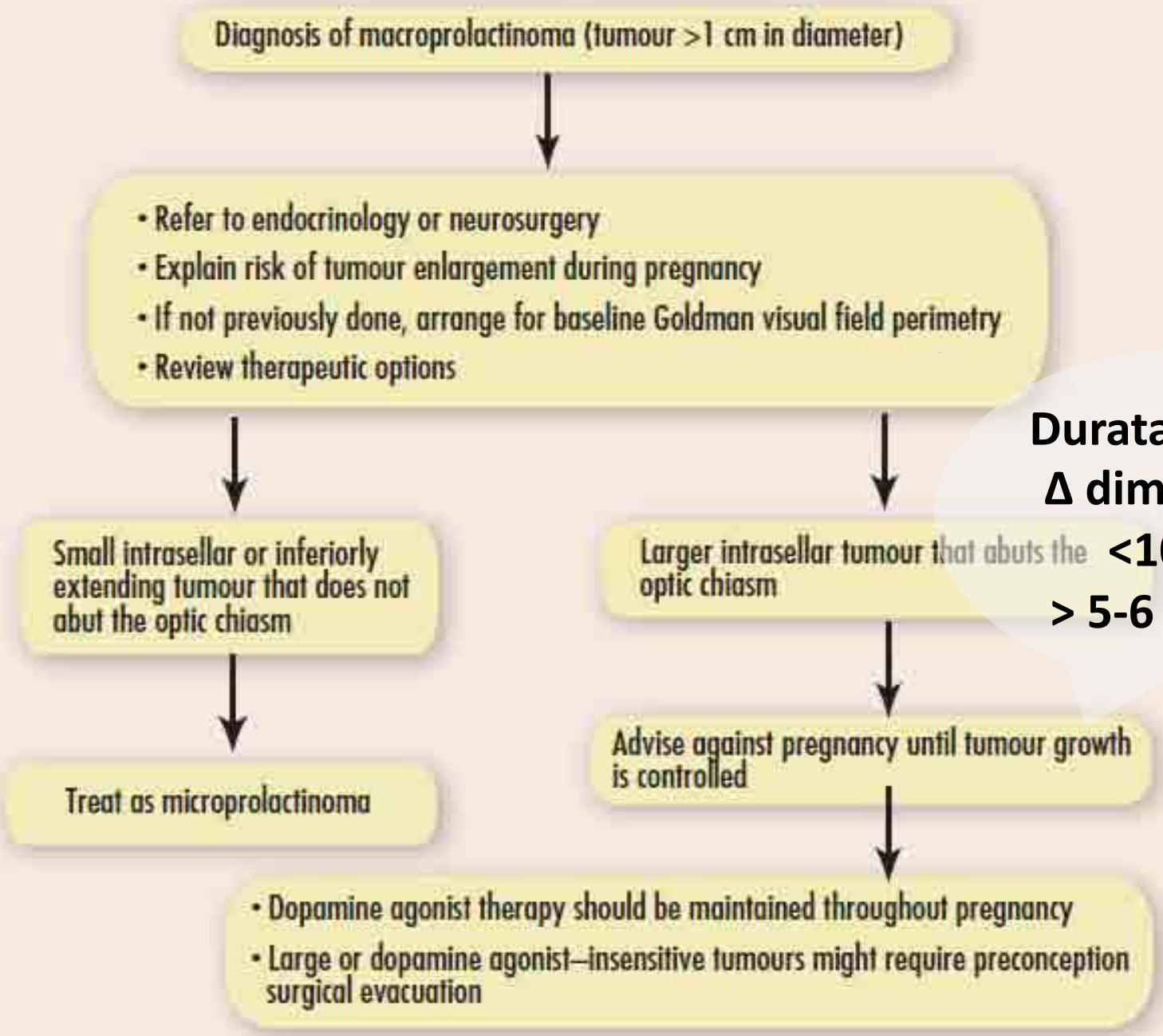
Table 4
Enlargement of prolactinomas during pregnancy.

Series	Ref. no.	Year	Microadenomas		Macroadenomas		Macroadenomas	
					No prior treatment		Prior treatment	
			Total	# Enlarged	Total	# Enlarged	Total	# Enlarged
Gemzell & Wang	54	1979	85	5	46	20	70	5
Molitch	55	1985	246	4	45	7	46	2
Holmgren et al.	56	1986	26	3	4	2	5	0
Ampudia et al.	57	1992	8	1	1	0	4	0
Kuppersmith et al.	59	1994	54	0	4	4	0	0
Rossi et al.	59	1995	22	2	3	1	2	0
Badawy et al.	60	1997	16	0	0	0	0	0
Mallmann et al.	61	2002	5	0	3	1	0	0
Bronstein et al.	35	2002	48	1	30	11	21	0
Ono et al.	40	2010	56	0	29	0	0	0
Lebbe et al.	41	2010	45	2	15	3	0	0
Stalldecker et al.	42	2010	47	0	34	0	0	0
Total			658	18 (2.7%)	214	49 (22.9%)	148	7 (4.8%)

There are two options for pregnant patients with macroprolactinoma. The first is to discontinue the dopamine agonist after confirmation of pregnancy with close follow-up. Monitoring should include screening for symptoms such as h
field examination
without a contrast
can be individualiz
be useful if the le
increasing tumor
rather than tumor
preferable in patie
nomas away from t
is continuing dop
pregnancy. The se

pregnancy. The second option may be preferred when the duration of dopamine agonist therapy before conception is short or when the tumor is outside intrasellar boundaries. If clinical signs of progression such as severe headache and visual field defects occur, an MRI without Gd should be performed, and then a dopamine agonist should be restarted if there is an increase in tumor size (143). If there is no response to dopamine agonist therapy, delivery may be the treatment of choice when the term is close. Transsphenoidal surgery can be performed on patients whose term is not close (144). Although good results have been reported with surgery, increased risk of spontaneous abortions should be kept in mind (145).

Figure 2. Approach to managing macroprolactinomas before pregnancy



Durata terapia?
Δ dimensioni?
<10 mm
> 5-6 mm O-P

ORIGINAL ARTICLE

Endocrine Care

J Clin Endocrinol Metab, June 2010, 95(6):2672–2679

Individualized High-Dose Cabergoline Therapy for Hyperprolactinemic Infertility in Women with Micro- and Macroprolactinomas

Masami Ono, Nobuhiro Miki, Kosaku Amano, Takakazu Kawamata, Toshiro Seki, Rena Makino, Kazue Takano, Shun-ichiro Izumi, Yoshikazu Okada, and Tomokatsu Hori

Discussion

The results of this study show that cabergoline can induce and promote successful pregnancy in a large majority of infertile women with prolactinoma irrespective of tumor size or bromocriptine resistance and intolerance. It is now apparent that cabergoline can correct hyperprolactinemia, recover fertility, induce pregnancy, control gestational tumor overgrowth, and bring about uneventful delivery in these infertile patients. Importantly, cabergoline provides this total care by itself without requiring any aid from gynecological, neurosurgical, and radiotherapeutic modalities. Our thera-

Colao study (22) (mean dose, 0.98 mg/wk). In comparison, the present study used a greater maximum dose, up to 9.0 mg/wk, with a higher mean dose of 2.29 mg/wk. No-

events in the mothers and fetuses. These results, obtained only from patients with prolactinoma in a single institution, further support the safety of cabergoline in pregnancy, even if used at higher than usual doses.

The third issue is symptomatic tumor enlargement during pregnancy. This is a serious complication that threat-

related to pregnancy (15, 19). In the present study, all 30 pregnancies that occurred in the 27 cabergoline-treated patients with macroadenomas had an uneventful course and outcome. It is likely that macroadenomas that con-

Table 3
Pregnancy outcomes summarized for women who became pregnant while taking bromocriptine[a] or cabergoline,[b] compare to what is expected in the normal population.[c]

	Bromocriptine (N)	Bromocriptine (%)	Cabergoline (N)	Cabergoline (%)	Normal (%)
Pregnancies	6239	100	789	100	100
Spontaneous abortions	620	9.9	60	7.6	10–15
Terminations	75	1.2	59[d]	7.5	20
Ectopic	31	0.5	3	0.4	1.0–1.5
Hydatidiform moles	11	0.2	1	0.1	0.1–0.15%
Deliveries (known duration)	4139	100	543	100	100
At term (>37 weeks)	3620	87.5	480[e]	88.4	87.3
Preterm (<37 weeks)	519	12.5	67	11.6	12.7
Deliveries (known outcome)	5120	100	471	100	100
Single births	5031	98.3	463	98.3	96.8
Multiple births	89	1.7	12	1.7	3.2
Babies (known details)	5213	100	664	100	100
Normal	5030	98.2	633	96.8	97
With malformations	93	1.8	21	3.2	3.0

Practice points

- Hyperprolactinemia is commonly associated with amenorrhea and infertility.
- Dopamine agonists are preferred to surgery to normalize prolactin levels.
- Cabergoline is more efficacious and better tolerated than bromocriptine.
- Both dopamine agonists are safe to use during the first few weeks of gestation to allow ovulation to occur, but the safety database for bromocriptine is much larger than that for cabergoline.
- Tumor enlargement can be seen in 2.7% of microadenomas, 22.9% of macroadenomas that had not had prior ablative treatment and 4.8% of macroadenomas that had prior ablative treatment.
- Patients should be followed carefully during pregnancy with symptom assessment and, for those with macroadenomas, visual field assessments.
- Symptomatic tumor growth can usually be successfully treated with reinstitution of the dopamine agonist; surgery is rarely necessary and delivery can be considered if the pregnancy is sufficiently advanced.

Wang et al. Systematic Reviews 2012, 1:33
http://www.systematicreviewsjournal.com/content/1/1/33

SYSTEMATIC REVIEWS

RESEARCH Open Access

Treatment of hyperprolactinemia: a systematic review and meta-analysis

Amy T Wang[1,2*], Rebecca J Mullan[1], Melanie A Lane[1], Ahmad Hazem[1,3], Chaithra Prasad[2], Nicola W Gathaiya[4], M Mercè Fernández-Balsells[1,5], Amy Bagatto[1], Fernando Coto-Yglesias[6], Jantey Carey[1], Tarig A Elraiyah[1], Patricia J Erwin[1], Gunjan Y Gandhi[7], Victor M Montori[1,4] and Mohammad Hassan Murad[1,3]

Pregnancy studies

Twenty studies followed pregnant women and their offspring from 6 months up to 12 years (Additional file 1: Table 7F). A fairly consistent finding was that there was no significant increase in the risk of obstetric complications, miscarriages, fetal malformation or other pregnancy outcomes, even if they had been treated with dopamine agonists to induce ovulation. The quality of this evidence is low considering the lack of contemporary untreated control groups in most studies or the enrollment of nonconsecutive samples of patients.

Bari,
7-10 novembre 2013

VIEWPOINT

The Optimal Practice of Evidence-Based Medicine
Incorporating Patient Preferences in Practice Guidelines

JAMA Published online October 28, 2013

Corresponding Author: Victor M. Montori, MD, MSc, Mayo Clinic, 200 First St SW, Plummer 3-35, Rochester, MN 55905 (montori.victor@mayo.edu).

Research evidence is necessary but insufficient for making patient care decisions. An effective but toxic chemotherapeutic regimen is the treatment one patient with cancer can and will take, another patient can take but will not, and yet another patient could not take even if wanted. Careful attention to the biopsychosocial context of patients and to their informed preferences when crafting treatments requires expertise and practical wisdom. This represents the optimal practice of evidence-based medicine.

PRL-omi e induzione della Gravidanza

Bari,
7-10 novembre 2013

Cabergoline for preventing ovarian hyperstimulation syndrome (Review)

Tang H, Hunter T, Hu Y, Zhai SD, Sheng X, Hart RJ

THE COCHRANE COLLABORATION®

Implications for practice

There is evidence that cabergoline reduces moderate OHSS but there is insufficient evidence that it reduces severe OHSS. The use of cabergoline does not influence the pregnancy outcome (clinical pregnancy rate, miscarriage rate).

Clin Invest Med • Vol 35, no 2, April 2012

Mussa H Almalki MBBS, SSC-MED, CABM, MHSc[1, 2]

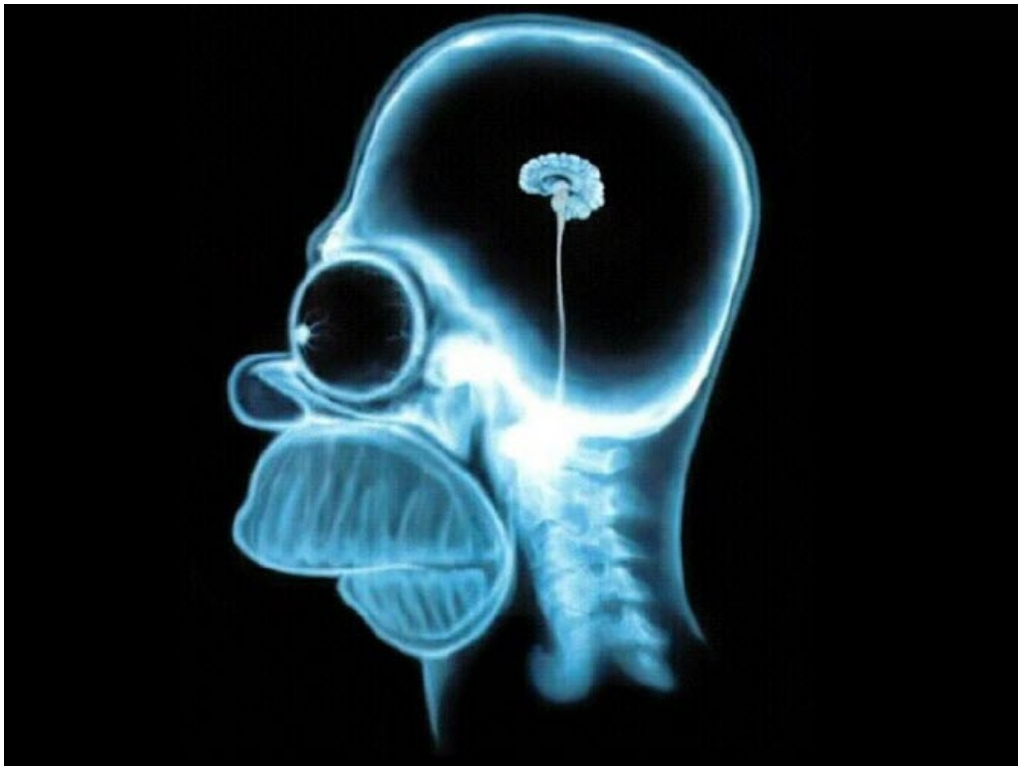
Management of prolactinomas during

TABLE 1: Case 1

TABLE 2: Case 2

MEDICAL MANAGEMENT:	Response rate (yes) (%)
Continue current dopamine agonist therapy throughout pregnancy.	6
Discontinue cabergoline and shift to bromocriptine due to better safety data.	29
Discontinue dopamine agonist therapy as soon as pregnancy is confirmed.	65
Refer for surgical excision of the tumor.	0
Recommend therapeutic abortion.	0
BIOCHEMICAL MONITORING:	
Continue regular monitoring of serum prolactin during pregnancy.	24
Discontinue monitoring serum prolactin during pregnancy.	64
Measure serum prolactin only if patient complains of new-onset headaches and/or vision changes.	12
PITUITARY IMAGING:	
Perform regular pituitary imaging during pregnancy to exclude tumor enlargement.	18
Perform pituitary imaging if serum prolactin is thought to be out of proportion with your clinical judgment.	12
Perform pituitary imaging only if patient complains of new-onset headaches and/or vision changes.	70
VISUAL FIELD TESTING:	
Perform regular formal visual field testing throughout pregnancy.	60
Perform formal visual filed testing only if patient complains of new-onset headaches and/or vision changes.	37
Never perform formal visual field testing.	0
Only perform informal (clinical) visual field testing.	3

Bari,
7-10 novembre 2013



Grazie per l'attenzione

Azienda Ospedaliera Sant'Andrea – Roma
UOC di Endocrinologia
Ambulatorio Patologia Ipofisaria
Cell 3395319652
ipofisi@ospedalesantandrea.it