SCIENTIFIC REPORT

Treatment of thyroid associated ophthalmopathy with periocular injections of triamcinolone

R Ebner, M H Devoto, D Weil, M Bordaberry, C Mir, H Martinez, L Bonelli, H Niepomniszcze

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Aim: To evaluate the efficacy of periocular triamcinolone acetonide for the treatment of thyroid associated ophthalmopathy (TAO), and the presence of ocular or systemic adverse effects.

Methods: A multicentre prospective pilot study was performed on patients diagnosed with Graves' ophthalmopathy less than 6 months before entry to the study. Patients were admitted to the study and were randomised into two groups: treatment and control. The treatment group received four doses of 20 mg of triamcinolone acetate 40 mg/ml in a peribulbar injection to the inferolateral orbital quadrant. Both groups were evaluated by measuring the area of binocular vision without diplopia on a Goldmann perimeter and the size of the extraocular muscles on computed tomography (CT) scans. Ophthalmological and systemic examinations were done to rule out ocular and systemic adverse effects. Follow up was 6 months for both groups.

Results: 50 patients were eligible for the study. 41 patients completed the study. There was an increase in the area of binocular vision without diplopia in the treatment group (Σ initial: mean 231.1 (SD 99.9) and final absolute change, mean 107.1 (SD 129.0)) compared to the control group (Σ initial: mean 350.7 (SD 86.5) and final absolute change, mean −4.5 (SD 67.6)). The sizes of the extraocular muscles were reduced in the treatment group (mean (inferior rectus initial values): 1.3 (0.7), final percentage change: −13.2 (25.7), medial rectus initial values: 1.2 (0.6), final percentage change: −8.2 (20.7), superior rectus-levator palpebrae initial values: 1.2 (0.6), final percentage change: −9.5 (29.1), lateral rectus initial values: 1.0 (0.4), final percentage change: −11.5 (20.6)) compared to the control group (inferior rectus initial values: 0.9 (0.3), final percentage change: −4.0 (21.5), medial rectus initial values: 0.9 (0.3), final percentage change: 0.6 (22.4), superior rectus-levator palpebrae initial values: 0.9 (0.3), final percentage change: 12.5 (37.5), lateral rectus initial values: 0.9 (0.4), final percentage change: −0.5 (31.6)). Both measurements (degree of diplopia and muscle thickness) were statistically significant between groups (initial − final). No systemic or ocular adverse effects were found.

Conclusions: Triamcinolone administered as a periocular injection is effective in reducing diplopia and the sizes of extraocular muscles in TAO ophthalmopathy of recent onset. This form of treatment is not associated with systemic or ocular side effects.

There is no gold standard of treatment for the thyroid associated ophthalmopathy (TAO) in the early (inflammatory) stages of the disease. Corticosteroids reduce the transitory manifestations of TAO but their multiple adverse effects make the risk/benefit relation unsatisfactory.[1–16]

The beneficial effects of steroids used locally (subconjunctival or retrobulbar injections) in the treatment of TAO have been reported in the literature.[17–26]

We are aware of no study designed to demonstrate the advantages of steroids used locally (periocular injections) improving TAO in the early stages. We also analysed the impact of secondary effects associated with local steroid administration. This multicentre, prospective pilot study was designed to evaluate this treatment.

METHODS

Fifty patients with TAO diagnosed between April 1998 and April 1999 were admitted to the study under the following inclusion criteria: TAO of 6 months' or less duration, with diplopia noticed either in primary position or at any position of regard. Exclusion criteria were previous treatment for TAO with steroids or radiation, compressive optic neuropathy, absence of diplopia, and contraindications to steroids (diabetes, systemic hypertension, gastritis, psychosis and pregnancy). Patients were included regardless their endocrine status.

They were randomised simply into two groups: group 1 (treatment group) received treatment with triamcinolone and group 2 (non-treatment group) received no treatment and acted as control group.

Patients were initially examined (week 0) for best corrected visual acuity (BCVA), measured in a decimal scale on a universal Snellen chart, intraocular pressure (IOP), measured in mm Hg with applanation tonometry, exophthalmometry (Ex), measured in mm with a Hertel exophthalmometer, optic nerve head examination (ON), graded as normal, papilloedema or optic nerve head atrophy. Total body weight (BW) were measured in kg and systemic systolic and diastolic arterial blood pressures (SBP, DBP) was measured in mm Hg. Ocular motility was measured with a Goldmann perimeter by a masked technician, according to Feibel and Roper-Hall methods.[27] The patient was positioned at the perimeter with both eyes uncovered. A 2-IV size light was used. It was moved along eight radial lines from the centre to the periphery and the patient was asked to say when double vision first appeared. A line was obtained encircling the area without diplopia. The summation of angular points was used for comparison (Σ).

The sizes of the four recti muscles were measured on computed tomography (CT) scans, coronal views, using a caliper. The scans selected for measurements were taken at the medial third of the orbit.

The size (diameter) of the optic nerve was used as a unit, dividing the measured size of each muscle by the size of the optic nerve, the ratio obtained was used for comparison. This

Abbreviations: BCVA, best corrected visual acuity; BW, body weight; DBP, diastolic blood pressure; IOP, intraocular pressure; ON, optic nerve; SBP, systolic blood pressure; TAO, thyroid associated ophthalmopathy

method was used to avoid bias when using CT scans printed with different magnifications. Measures were made by an unmasked physician.

Blood tests were done for glycaemia (Gl), calcaemia (Ca), plasma cortisol (Cpl), and urinary cortisol (Cur). Normal values were adopted from those used at the Massachusetts General Hospital Laboratory.

Patients in the treatment group were treated with four injections of triamcinolone acetonide (Kenacort A, 40 mg/ml, Bristol-Meyers-Squibb) of 20 mg in each orbit administered weekly during 4 consecutive weeks (weeks 1, 2, 3, and 4). The injected compound represents a deposit formulation of triamcinolone.

The injection was placed in the inferior lateral quadrant of the orbit using a 27 gauge half inch disposable needle.

Before each injection, IOP, SBP, DBP, and BW were recorded.

Both groups were followed at week 10, measuring SBP, DBP, BW, BCVA, IOP, Ex, and NO. Ocular motility and blood tests were also recorded (Gl, Ca, Cpl, and Cur). At week 24 both groups were examined for BCVA, IOP, Ex, ON, ocular motility, and muscle sizes on a new CT scan.

Results were compared for both groups using Student's *t* test. Blood tests were defined as normal or abnormal, calculating the median for each value. Additional statistical analysis was performed (Dunnet T test, test of comparison of treatment versus control and analysis of log normal distribution).

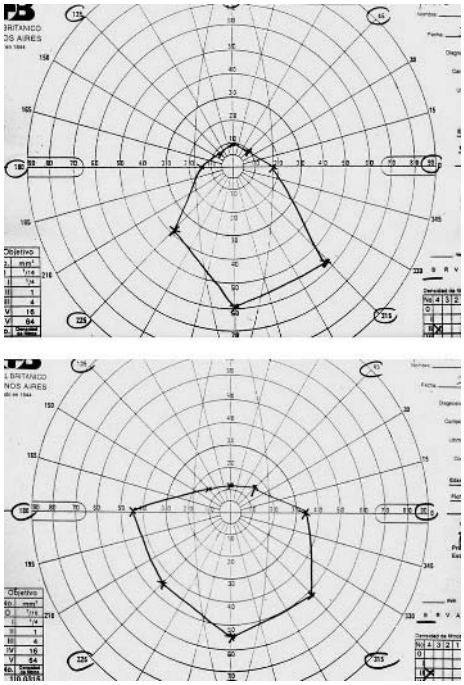

Figure 1 (A) Area of non-diplopia acquired with Goldmann perimeter, the treatment group patient before treatment. (B) Improvement in the area of non-diplopia of same the treatment group patient at week 24.

RESULTS

From the 50 enrolled patients, five were excluded from the analysis as a result of violations to the protocol or were withdrawn. Therefore, 45 patients were available for safety analyses (25 in the treatment group and 20 in the non-treatment group). From them, 41 patients were available for efficacy analyses (24 in the treatment group and 17 in the non-treatment group).

Table 1 Major demographic features—safety population

Demographic feature	Treatment group (n = 25)	Non-treatment group * (n = 20)	Difference between groups
Age (years)			p = 0.0017
Mean (SD)	50.3 (13.3)	36.1 (15.2)	
Range	(22–78)	(11–62)	
Sex			p = 0.4283†
Number (%)			
Male	9 (36.0%)	5 (25.0%)	
Female	16 (64.0%)	15 (75.0%)	
Body weight (kg)			p = 0.4353†
Mean (SD)	67.5 (14.2)	63.3 (20.9)	
Range	(47–111)	(40–132)	

*n = 19 for body weight; †not significant.

Table 2 Ocular motility area of no diplopia (Σ°)—efficacy population

Ocular motility	Treatment group	Non-treatment group	Difference between groups
Week 0			p = 0.0005
Mean (SD)	231.1 (99.9)	350.7 (86.5)	
Range	(40–398)	(185–485)	
Number	20	17	
Week 10, absolute change			p = 0.0072
Mean (SD)	93.6 (129.4)	1.18 (39.1)	
Range	(−60.0–517.0)	(−77.0–82.0)	
Number	20	17	
Week 24, absolute change			p = 0.0048
Mean (SD)	107.1 (129.0)	−4.5 (67.6)	
Range	(−20.0–497.0)	(−181.0–118.0)	
Number	19	15	

Table 3 Ocular motility area of no diplopia (Σ°): analysis of covariance—efficacy population

Ocular motility	Treatment group	Non-treatment group	Difference between groups
Week 10, absolute change			p = 0.2972*
LS mean (SE)	68.4 (22.1)	30.7 (24.3)	
Number	20	17	
Week 24, absolute change			p = 0.2899*
LS mean (SE)	76.4 (23.6)	34.3 (27.1)	
Number	19	15	

*Not significant; LS, mean least square mean from model.
Week 10 *v* week 0: p = 0.0081.
Week 24 *v* week 0: p = 0.0032.

Table 4 Ocular motility area of no diplopia (Σ°)—patients with Σ° between 200° and 400° at baseline—efficacy population

Ocular motility	Treatment group	Non-treatment group	Difference between groups
Week 0			p = 0.3290*
Mean (SD)	304.5 (59.3)	329.7 (61.0)	
Range	(216–398)	(205–387)	
Number	11	12	
Week 10, absolute change			p = 0.0060
Mean (SD)	72.3 (63.3)	−4.17 (39.2)	
Range	(−4.0–225.0)	(−77.0–63.0)	
Number	11	12	
Week 24, absolute change			
Mean (SD)	79.2 (69.3)	−11.1 (75.5)	p = 0.0122
Range	(−10.0–189.0)	(−181.0–118.0)	
Number	10	10	

*Not significant.

From the efficacy population of 41, 37 patients were available for ocular motility evaluation (20 in the treatment group and 17 in the non-treatment group) and other 37 (23 in the treatment group and 14 the non-treatment group) were available for muscle size evaluation. Table 1 depicts the distribution of the safety population according to age, weight, and sex.

The analysis of motility showed that the treatment group had a mean Σ of 231.1 (SD 99.9) and the non-treatment group a mean Σ of 350.7 (86.5) at baseline. At week 10, the treatment group mean absolute change was 93.6 (SD 129.4), showing an improvement of 91.56%, and the non-treatment group mean absolute change was 1.18 (39.1), a change of 2%. At week 24, the treatment group mean absolute change was 107.1 (SD 129.0) showing an improvement of 105.93%, the non-treatment group mean absolute change was −4.5 (67.6), a change of 1.30% (see fig 1 and table 2).

In this pilot study, the treatment group and the non-treatment group differed initially in motility (p = 0.0005); therefore, we conducted a second exploratory analysis of the data of: A, the entire efficacy population; and B, a population were the motility disturbances were not observed in the primary position (or permanent diplopia), or manifest only in the extremes positions of regard. A covariance analysis was applied. The results obtained in A showed no significant statistical differences between groups but statistical significant differences were observed between weeks 0 and 24 (tables 2 and 3). For B, Σ initial mean value (SD) was 304.5 (59.3) for the treatment group (n = 11), and 329.7 (61.0) for the non-treatment group (n = 12); no statistical significant differences between groups were detected (p = 0.3290). At week 10, the treatment group absolute change mean (SD) was 72.3 (63.3), a change of 30.03%, and the non-treatment group absolute change mean (SD) was −4.17 (39.2), a change of −0.59%. Statistically significant differences were detected between groups (p = 0.0060). At week 24, the treatment group absolute change mean (SD) was 79.2 (69.3) with a change of 31.45%, and the non-treatment

Table 5 Ocular motility area of no diplopia (Σ°): patients with Σ° between 200° and 400° at baseline, analysis of covariance—efficacy population

Ocular motility	Treatment group	Non-treatment group	Difference between groups
Week 10, absolute change			
LS mean (SE)	66.5 (14.0)	1.2 (13.4)	p = 0.0033
Number	11	12	
Week 24, absolute change			
LS mean (SE)	71.5 (23.6)	−3.4 (20.1)	p = 0.0184
Number	10	10	

LS, mean least square mean from model.
Week 10 *v* week 0: p = 0.0146.
Week 24 *v* week 0: p = 0.0176.

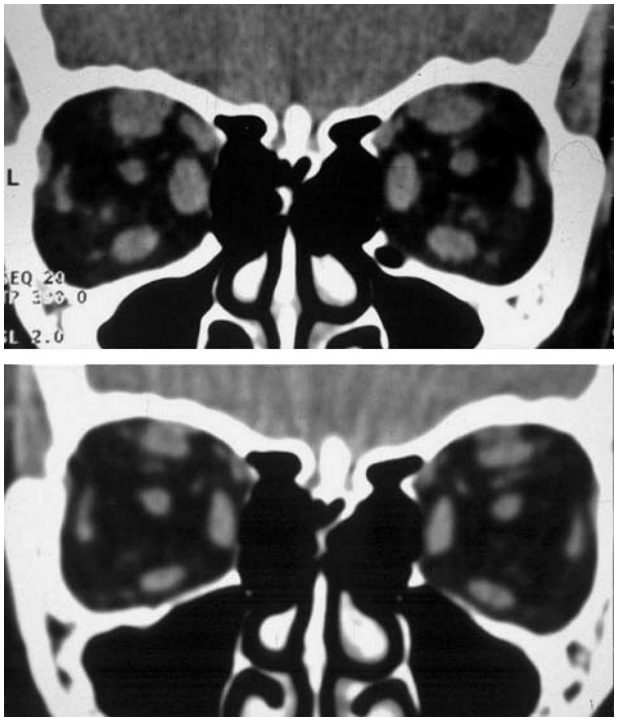

Figure 2 (A) CT scan coronal views of extraocular muscles in the treatment group patient before treatment. (B) CT scan coronal views of extraocular muscles of the same treatment group patient at week 24.

group absolute change mean (SD) was −11.1 (75.5) with a change of −1.91%. Statistically significant differences were detected between groups (p = 0.0122). Analysis of covariance for this population showed statistically non-significant differences between groups at baseline and significant differences between weeks 10 and 24 (see tables 4 and 5).

Measurements of extraocular muscles showed the following variations between week 0 and 24: for the inferior rectus muscle, in the treatment group percentage change mean (SD) was −13.21 (25.7) and the non-treatment group percentage change mean (SD) was −4.02 (21.5); no statistically significant differences were detected between groups. For the medial rectus muscle, the treatment group percentage change mean (SD) was −8.24 (20.75) and the non-treatment group percentage change mean (SD) was −0.6 (22.39); no statistically significant differences were detected between groups. For the lateral rectus muscle the treatment group percentage change mean (SD) was −11.5 (20.6) and the non-treatment group percentage change mean (SD) was −0.5 (31.6), no statistically differences were detected between groups. For the superior rectus muscle-levator complex, the treatment group percentage change mean (SD) was −9.5 (29.1) and the non-treatment group percentage mean change (SD) was 12.54 (37.5); statistically significant differences were detected between groups (p = 0. 0060) (fig 2 and table 6).

No variations were detected between groups related to BCVA, IOP, Ex, BW, and BP at weeks 10 and 24.

There were no variations in blood levels of glycaemia, calcaemia, and cortisol (table 7).

Urinary cortisol showed a difference in the treatment group between week 0 and week 10. Since these values are not normally distributed, their results were analysed using a logarithmic transformation that showed a geometric mean value of −31.58% (p = 0.114) for the treatment group and −3.75% (p = 0.842) for the non-treatment group in week 10 (table 8).

No adverse effects related to the injection were encountered. Figure 3 illustrates the facial aspect of a the treatment group patient at week 0 and 24.

Table 6 Thickness variations of extraocular muscles relative to optic nerve size—efficacy population

Muscles	Treatment group* (n = 46)	Non-treatment group (n = 28)	Difference between groups
Inferior rectus:			
Week 0			p = 0.0184
Mean (SD)	1.3 (0.7)	0.9 (0.3)	
Range	(0.4–3.2)	(0.3–2.0)	
Week 24, percentage change			p = 0.1173†
Mean (SD)	−13.2 (25.7)	−4.0 (21.5)	
Range	(−60.6–69.1)	(−63.6–42.6)	
Medial rectus:			
Week 0			p = 0.0153
Mean (SD)	1.2 (0.6)	0.9 (0.3)	
Range	(0.5–3.1)	(0.5–1.5)	
Week 24, percentage change			p = 0.0900†
Mean (SD)	−8.2 (20.7)	0.6 (22.4)	
Range	(−42.8–42.8)	(−27.8–66.7)	
SRLP:			
Week 0			p = 0.0506†
Mean (SD)	1.2 (0.6)	0.9 (0.3)	
Range	(0.5–3.2)	(0.5–1.8)	
Week 24, percentage change			p = 0.0060
Mean (SD)	−9.5 (29.1)	12.5 (37.5)	
Range	(−63.8–78.6)	(−41.7–139.2)	
Lateral rectus:			
Week 0			p = 0.0662†
Mean (SD)	1.0 (0.4)	0.9 (0.4)	
Range	(0.4–2.1)	(0.4–1.8)	
Week 24, percentage change			p = 0.0765†
Mean (SD)	−11.5 (20.6)	−0.5 (31.6)	
Range	(−63.1–39.2)	(−51.6–87.5)	

n, number of eyes; *n = 45 for lateral rectus; †not significant.

Table 7 Calcaemia, glycaemia, and plasma cortisol variations—safety population

Laboratory tests	Treatment group	Non-treatment group
Calcaemia (mg/dl)		
Week 0		
Mean (SD)	9.1 (0.5)	9.0 (0.8)
Range	(8.3–10.1)	(7.8–10.3)
Number	25	20
Week 10		
Mean (SD)	8.9 (0.3)	9.1 (0.6)
Range	(8.3–9.6)	(8.1–10.0)
Number	23	17
Glycaemia (mg/dl)		
Week 0		
Mean (SD)	96.2 (15.3)	92.8 (24.3)
Range	(70.0–146.0)	(71.0–186.0)
Number	25	20
Week 10		
Mean (SD)	90.1 (16.7)	86.8 (8.3)
Range	(62–134)	(70.0–100.0)
Number	22	17
Plasma cortisol (µg/dl)		
Week 0		
Mean (SD)	17.2 (5.5)	19.0 (10.5)
Range	(6.0–30.7)	(6.0–37.4)
Number	24	20
Week 10		
Mean (SD)	14.6 (5.0)	22.9 (16.6)
Range	(6.0–25.3)	(6.2–71.1)
Number	22	16

DISCUSSION

The use of methyl prednisone and triamcinolone as an intraorbital or subconjunctival injection has already been reported.[17–26]

Triamcinolone is a synthetic glucocorticosteroid with a potency that equals five times that of cortisol, is metabolised in the liver (tetrahydrocortisol), and excreted as a soluble compound in the urine. It is fluorated in position 9 of the second ring giving it a marked glucocorticoid activity, and a reduced mineralocorticoid activity due to a OH substitution at C16.[28 29]

The administration by a peribulbar injection in the inferior-lateral quadrant of the orbit allows its diffusion in the retrobulbar fat to the extraocular muscles[30 31]

Multiple complications have been reported with periocular injections of steroids, including globe perforation,[32–36] arterial occlusion,[37] toxic optic neuropathy,[38] or atrophy of subcutaneous tissue in the face.[39 40] We did not encounter any of these problems in our series.

The use of locally administered steroids has been previously reported as beneficial.[17–26] Trobe *et al* have reported unfavourable outcomes in patients with compressive optic neuropathy.[24] We have excluded this group of patients from our study.

Sergott and Glaser[7] and Lee and Brazis[41] warn against their use, based on the lack of studies that demonstrate an improvement in Graves' ophthalmopathy by local steroids. They are concerned by the increase in volume produced by an injection in a congested orbit.

In this study, we have used triamcinolone injected intraorbitally, and demonstrated an improvement in motility, particularly for the group of patients with non-permanent diplopia (diplopia in eccentric gaze) and a reduction in the extraocular muscle sizes. Best corrected visual acuity has remained unchanged, as well as IOP, exophthalmos, and optic nerve head examination. There were no changes in body weight or blood pressure. Systemic glycaemia, calcaemia, and cortisol remained within normal values for the treatment group and the non-treatment group throughout the study. Urinary cortisol was reduced in 31.58% in the treatment group compared with 3.52% in the non-treatment group . Although these values were not statistically significant, they might suggest a mild depression in endogenous production of cortisol.

Table 8 Urinary cortisol (µg/24 hours)—safety population

Urinary cortisol (µg/24 hours)	Treatment group (n = 21)	Non-treatment group (n = 15)	Difference between groups
Week 0			p = 0.0582*
GM	43.4	75.9	
(GM−SD; GM+SD)	(18.2; 103.6)	(34.0; 169.2)	
Range	(4–207)	(20–406)	p = 0.0070
Week 10			
GM	29.7	73.0	
(GM−SD; GM+SD)	(9.4; 93.3)	(46.0; 115.9)	
Range	(3–295)	(34–204)	
Week 10, percentage change			p = 0.2869*
GM	−31.6	−3.8	
(GM−SD; GM+SD)	(−76.1; 95.9)	(−53.6; 99.6)	

GM, geometric mean; *not significant.

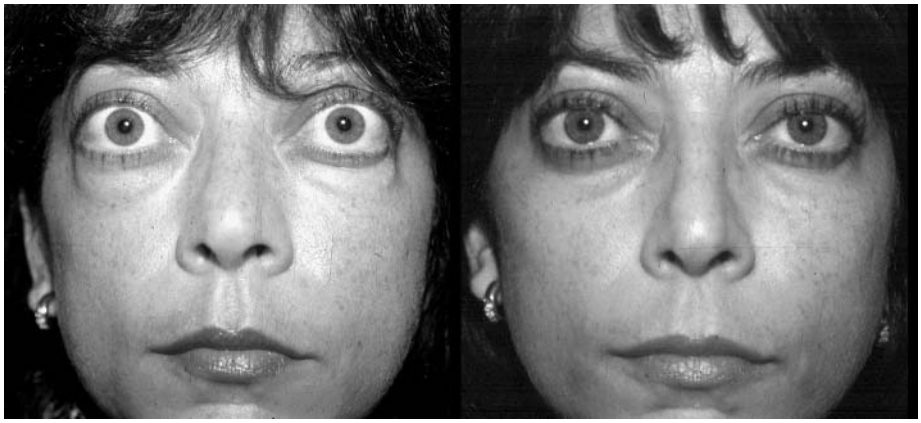

Figure 3 (A) Treatment group patient, facial aspect before treatment. (B) Same patent at week 24.

We demonstrate in this study the favourable effects of triamcinolone administered as a periocular injection in TAO. Relative to the control group, patients receiving triamcinolone had less diplopia and smaller extraocular muscles. We noted no secondary effects due to the steroid and no local complications caused by the procedure. Owing to the small number of patients entered in this pilot study, a larger series is required to confirm our results.

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Authors' affiliations

R Ebner, Unidad de Neurooftalmología, Hospital Británico de Buenos Aires, Argentina
M H Devoto, Consultores Oftalmológicos, Buenos Aires, Argentina
D Weil, H Martinez, L Bonelli, Sección Orbita, Hospital de Clínicas, Buenos Aires, Argentina
M Bordaberry, Hospital Centenario, Universidad Nacional de Rosario, Argentina
C Mir, Hospital Central de Mendoza, Universidad de Cuyo, Argentina
H Niepomniszcze, Seccion Tiroides, Hospital de Clinicas, Buenos Aires, Argentina

Correspondence to: Roberto Ebner, MD, Coronel Díaz 2277 5toD, (1425) Capital Federal, Buenos Aires, Argentina; rebner@intramed.net.ar

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The Lighter Side

World sit-up champion Sue Prion delivers her first baby. © Michael Balis.