Epidemiologic aspects of postpartum pituitary hypofunction (Sheehan's syndrome)

Two hundred seventy-nine (3.20%) of the 8,730 parous females aged 20–39 years and 124 (4.18%) of 2,970 parous females aged 40 years or older who were screened were suspected to have Sheehan's syndrome; 115 and 55 of these females in the two age groups were fully evaluated, and 98 and 51 of them, respectively, were proven to have Sheehan's syndrome. At these rates, the projected number of women with Sheehan's syndrome among a total population of parous females aged ≥20 years (12,32,827, as per census data) would be 38,691 in the Kashmir valley of the Indian subcontinent. (Fertil Steril® 2005;84:523–8. ©2005 by American Society for Reproductive Medicine.)

Sheehan's syndrome (SS) refers to varying grades of anterior pituitary hormone deficiency resulting from infarction of the physiologically enlarged pituitary gland of pregnancy after postpartum hemorrhage (PPH) and consequent circulatory failure (1). Because the risk of obstetric hemorrhage resulting in significant hypotension is much greater in developing countries, the majority of cases of SS occur in these countries; the sheer numbers of women residing in these regions of the world make SS the commonest cause of hypopituitarism worldwide (2). The National Family Health Survey in India (1998–1999) revealed that 66% of the deliveries occurred at home, and the incidence of PPH was 11% (3). The degree of hypopituitarism in SS is highly variable. Partial or complete spontaneous recovery does take place in some cases, and subsequent pregnancy has been reported (4).

There are no clear data available on the incidence and prevalence of SS, largely because it has become almost extinct in the developed world. We have been, for more than a decade, diagnosing SS in an increasing number of women who are suspected to have SS by primary care doctors who have become sensitized to the condition over the years; this prompted us to design a study to estimate the prevalence of SS in the Kashmir valley of the Indian subcontinent.

This study was conducted to estimate the prevalence of SS in the Kashmir valley. The study protocol was approved by the institutional review board. A total of 11,700 females who attended the six district hospitals of the Kashmir valley were interviewed for any history of PPH (defined as loss of >500 mL of blood during the first 24 hours after delivery), the need for blood transfusion, and/or failure to lactate or menstrual disturbances after the last delivery. All females with such a history were clinically assessed for evidence of pituitary hypofunction and were requested to attend our center for evaluation. Any female who was known to have pituitary disease or any other endocrine disorder, whether or not on treatment, was excluded at initial screening.

Four hundred three (3.44%) of the 11,700 females screened were recruited for further evaluation (359 who had a history of PPH and 44 who had no history of PPH but had some suggestion of hypopituitarism after their last delivery). Only 196 of these 403 females turned up and consented for evaluation and received a complete clinical assessment with particular emphasis on lactotroph, somatotroph, gonadotroph, thyrotroph, and corticotroph hypofunction.

The laboratory evaluation included routine investigations (complete blood count, urinalysis, serum chemistry, electrocardiogram, and radiographs of chest and skull) and endocrine evaluation, including basal levels of serum T3, T4, TSH, LH, FSH, GH, cortisol, and PRL and levels of the last five hormones after appropriate provocative tests (insulin tolerance, metoclopramide, chlorpromazine, and clomiphene citrate stimulation tests) (5, 6). All hormone estimations were performed by specific RIA.

Computed tomography and/or magnetic resonance imaging scans of the head were performed in most subjects. The criteria used to diagnose SS included the following: [1] history of PPH or of absent or inadequate lactation or of menstrual disturbances after last delivery, [2] clinical evidence of deficiency of one or more pituitary hormones, [3] laboratory documentation of deficiency of at least one pituitary hormone, and [4] absence of any clinical or radiological suggestion of pituitary mass lesion (7). Statistical analysis was performed by the Windows version of SPSS, release 10.0.1 (SPSS Inc., Chicago, IL).

Of the 11,700 parous females screened in the initial field survey, 7,525 (65%) were from rural areas (Table 1), and

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TABLE 1

Areawise distribution of 11,700 females screened.

Area	No. screened (%)	No. enrolled (%)	No. with PPH (%)
Rural	7,525 (64.32)	274 (68.0)	251 (69.92)
Semiurban and urban	4,175 (35.68)	129 (32.0)	108 (30.08)
Total	11,700 (100)	403 (100)	359 (100)

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8,730 (75%) were younger than age 40 years. The demographic characteristics of subjects enrolled (n = 403), actually evaluated (n = 196), finally analyzed (n = 170; 26 excluded because of inadequate data), and proved to have SS (n = 149) were comparable (Table 2). The percentage of women with signs and symptoms suggesting various pituitary hormone deficiencies among women initially enrolled and actually studied are shown in Table 3.

Of the 149 females proved to have SS, 98 (66%) were younger than 40 years, 101 were from rural areas, 94 had a home delivery, and only 131 had history of PPH (Table 2). Of these, 26, 35, 28, 26, and 34 females had deficiency of one, two, three, four, and five trophic hormones, respectively (Figure 1 and Table 4). The number of deficient trophic hormones was influenced by age at evaluation, parity, and time since last delivery, the last factor attesting to the slowly progressive evolution of this disorder (Figures 2–4). Among women with one trophic hormone deficiency, the mean age at evaluation, parity, and time since last delivery were 32.46 ± 8.30, 3.04 ± 2.16 , and 5.62 ± 4.66 years, respectively; the corresponding figures for women with five trophic hormone deficiencies were 38.77 ± 8.69, 4.19 ± 2.74, and 9.74 ± 8.05 years, respectively (*P* values <.035, .351, and .004, respectively). Prolactin, gonadotropin, GH, TSH, and ACTH deficiency were documented, respectively, in 85.2%, 80.5%, 59.7%, 57.7%, and 53.7% of 149 females with SS.

Of 8,730 parous females aged 20–39 years who were screened, 279 (3.20%) were enrolled for pituitary function evaluation; of 115 such females actually evaluated adequately, 98 (85.22%) were documented to have SS. At these rates, the estimated number of women with SS among a total population of 20- to 39-year-old parous females of 786,426 would be about 21,410. Similarly, of the 2,970 parous females aged 40 years or older who were screened, 124 (4.18%) were enrolled; of 55 such females actually analyzed, 51 (92.73%) were documented to have SS. Given a total population of 446,401 parous females aged ≥40 years, the number of women with SS among them would be about 17,281, giving a total estimated number of women with SS among parous females aged ≥20 years of 38,691, making SS an important public health problem (8).

This study gives the first population-based profile of SS. We assume that our results should be representative of the

TABLE 2

Demographic characteristics of females enrolled, evaluated, included in final results, and proved to have SS.

Subject group	Age in y, mean ± SD (range)	Parity, mean ± SD (range)	Rural/ semiurban/ urban	Last delivery at home/ hospital	History of PPH	Time since last delivery in y, mean ± SD (range)
Enrolled (n = 403)	36.14 ± 8.68 (19–62)	3.56 ± 2.12 (1–13)	274/65/64	254/149	359	6.92 ± 5.91 (1–30)
Evaluated (n = 196)	34.96 ± 8.46 (20–60)	3.33 ± 2.16 (1–12)	128/20/48	120/76	170	6.85 ± 5.85 (1–30)
Finally reported (n = 170)	35.42 ± 8.61 (20–60)	3.15 ± 1.81 (1–12)	112/12/46	102/68	143	6.98 ± 5.81 (1–30)
Documented Sheehan's syndrome (n = 149)	35.96 ± 8.84 (20–60)	3.29 ± 1.84 (1–12)	101/10/38	94/25	131	7.27 ± 6.01 (1–30)

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TABLE 3

Prevalence of signs and symptoms in females enrolled and females finally evaluated.

Sign or symptom	Subjects enrolled (n = 403)	Subjects who didn't turn up (n = 207)	Subjects evaluated (n = 196)	*P* value
Lactotroph failure				
Complete alactation	190 (47.1)	83 (40.1)	107 (54.5)	.004[a]
Inadequate lactation	88 (21.8)	52 (25.1)	36 (18.3)	.105
Gonadotroph failure				
Amenorrhea	203 (51.6)	106 (51.2)	102 (52.4)	.873
Oligomenorrhea	64 (17.4)	31 (15.0)	39 (19.9)	.187
Regression of secondary sexual characteristics	198 (49.1)	92 (44.4)	106 (54.1)	.293
Corticotroph failure				
Hypotension	154 (38.2)	74 (35.7)	80 (40.8)	.293
Asthenia	120 (31.2)	50 (24.2)	76 (38.7)	.002[a]
Anorexia	86 (21.3)	35 (16.9)	51 (26.1)	.026
Weakness	305 (75.9)	159 (76.8)	146 (74.4)	.591
Thyrotroph failure				
Cold intolerance	215 (53.3)	100 (48.3)	115 (58.6)	.037
Somnolence	186 (46.1)	105 (50.7)	81 (41.3)	.059
Lethargy	312 (77.4)	164 (79.2)	148 (75.1)	.375
Dry skin	104 (25.8)	55 (26.6)	49 (25.0)	.818
Hung up jerks	183 (45.4)	87 (42.0)	96 (48.9)	.159

Note: Data in parentheses are percentages. Percentages were comparable except for alactation, asthenia, and anorexia, where a greater proportion turned up for evaluation.

[a] Statistically significant.

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TABLE 4

Correlation between the extent of hypopituitarism and age at evaluation, parity, and time since last delivery in 149 females with documented Sheehan's syndrome.

Variable	No. of patients (%)	Age in y at evaluation, mean ± SD (range)	Parity, mean ± SD (range)	Time in y since last delivery, mean ± SD (range)
Extent of hypopituitarism				
a) One-hormone deficiency	26 (17.45)	32.46 ± 8.30 (22–50)	3.04 ± 2.16 (1–12)	5.62 ± 4.66 (2–25)
b) Two-hormone deficiency	35 (23.5)	33.57 ± 8.11 (22–60)	3.06 ± 1.71 (1–7)	4.97 ± 3.86 (1–17)
c) Three-hormone deficiency	28 (18.8)	36.04 ± 8.61 (20–58)	3.39 ± 1.83 (1–7)	6.89 ± 4.65 (2–16)
d) Four-hormone deficiency	26 (17.45)	36.50 ± 9.56 (25–60)	3.19 ± 1.92 (1–8)	8.73 ± 6.76 (2–28)
e) Five (all)-hormone deficiency	34 (22.8)	38.77 ± 8.69 (22–55)	4.19 ± 2.74 (1–12)	9.74 ± 8.05 (1–30)
P a vs. e		<.035 (S)	.351 (NS)	.004 (S)

Note: S = significant; NS = not significant.

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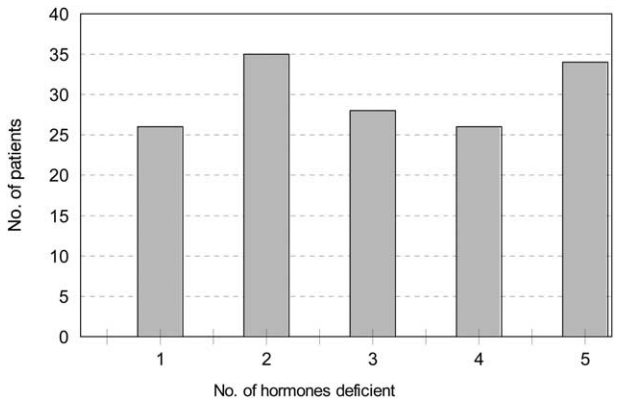
FIGURE 1

Showing the number of deficient trophic hormones in 149 females with SS.



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Indian subcontinent and other developing countries of the world. In 1996, we published a series of 86 women diagnosed with SS at our center over a period of a decade, from January 1985 to December 1994 (9). Famuyiva and coworkers in 1992 (10) reported that over a period of 5 years (December 1979 to December 1984), only 11 cases of SS were diagnosed at a teaching hospital in Nigeria, and in the previous 2 decades, there had been only 28 documented accounts of SS in Africans. They attributed this apparent rarity of SS in a developing region with a poor level of obstetric care to poor medical care (causing death of many of these patients from vascular shock and acute pituitary insufficiency before reaching a hospital or from chronic pituitary insufficiency while under care of a traditional faith healer), overreliance on clinical features for diagnosis in absence of adequate facilities for endocrinologic evaluation (necessitating a high index of suspicion and a strong clinical acumen and therefore making it likely that mild and subclinical cases were missed), clinical mimicry (causing such misdiagnoses as psychiatric problems, renal failure, anemia), and relatively long incubation period of the syndrome.

The demographic characteristics of our patients with SS were similar to those reported for women from Africa and other parts of India (10, 11). As reported in earlier studies, not all of our subjects had PPH (9, 11). The causative mechanisms proposed to explain postpartum pituitary necrosis in the absence of PPH include generalized Schwartzman phenomenon, disseminated intravascular coagulation, and autoimmunity.

We conclude that SS is a widely prevalent problem in our part of the world. Because of its varied presentation and socioculturally based reluctance of our patients to volunteer reproductive dysfunction details, we must have a low threshold for suspecting this condition. Massive improvements in medical care in general and in obstetric care in particular are required to contain this problem of enormous medical and social costs.

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FIGURE 2

Age vs. hormone deficiency. Hormone deficiency = .75823 + .04661 × age. Correlation: r = .24119.

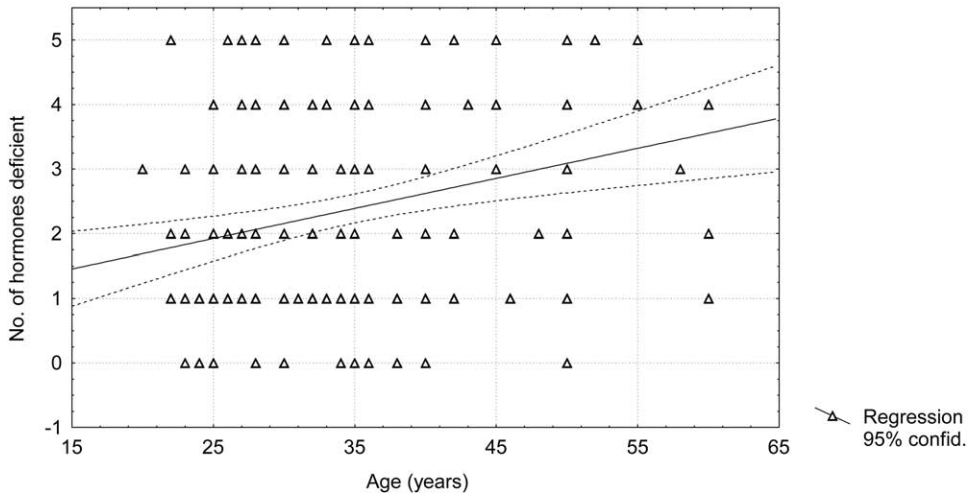

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FIGURE 3

Parity vs. hormone deficiency. Hormone deficiency = 1.7227 + .36820 × parity. Correlation: r = .16975.

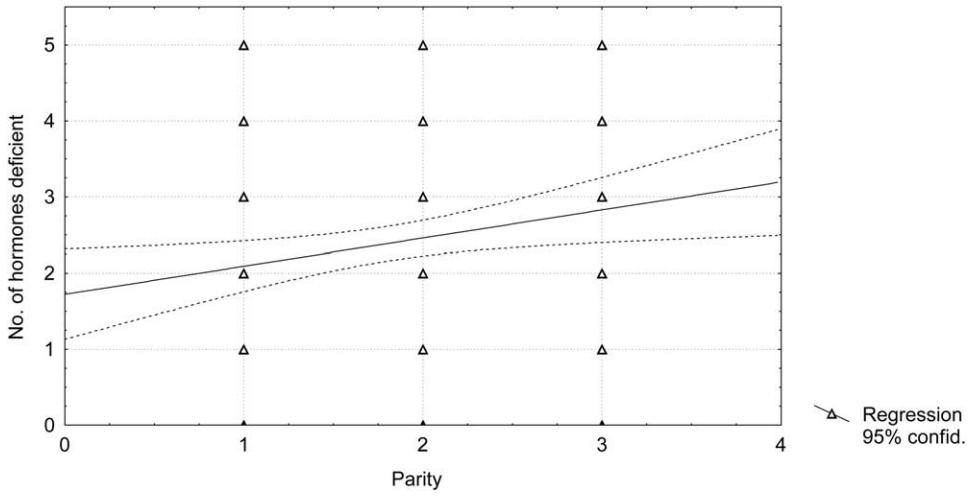

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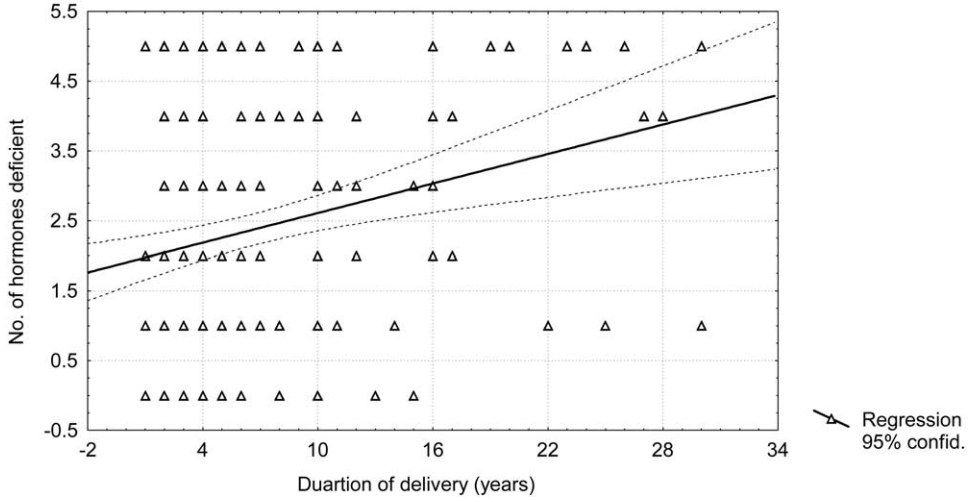
FIGURE 4

Duration of delivery vs. hormone deficiency. Hormone deficiency = 1.9038 + .07052 × duration. Correlation: r = .25247.



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