Clinical Neurology and Neurosurgery 176 (2019) 53–60

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Fertility after transsphenoidal surgery in patients with prolactinomas: A meta-analysis

Nayan Lamba[a,1], Nadia Noormohamed[b,1], Thomas Simjian[b], Mona Y. Alsheikh[b], Alykhan Jamal[b], Joanne Doucette[b], Hasan Zaidi[a], Timothy R. Smith[a,2], Rania A. Mekary[a,b,*,2]

[a] Computational Neuroscience Outcomes Center, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[b] School of Pharmacy, MCPHS University, Boston, MA, USA[3]

ARTICLE INFO

Keywords:
Prolactinoma
Transsphenoidal surgery
Fertility
Galactorrhea
Amenorrhea
Meta-analysis

ABSTRACT

Pituitary prolactinomas in women often lead to amenorrhea, galactorrhea, or infertility. The purpose of this study was to evaluate the effectiveness of transsphenoidal surgery (TSS) in restoring fertility in women with proloactinomas. A systematic search of the literature was conducted in accordance with PRISMA guidelines through 6/13/2017. PubMed, Embase, and Cochrane databases were utilized to select studies reporting on patients with pituitary prolactinomas removed via TSS. Outcomes extracted included pre- and post-operative rates of menses, lactation, and fertility. Pooled effect estimates were calculated using random-effects. After removal of duplicates, 900 articles remained, of which 14 were meta-analyzed. The mean difference between pre- and post-operative prolactin level was 186.9 (95% CI = 133.7, 240.1; I^2 = 69.9%; P-heterogeneity < 0.01; 7 studies). The pooled prevalence of pre-operative amenorrhea was 96% (95% CI = 92%, 98%; I^2 = 45.8%; P-heterogeneity = 0.09; 11 studies) and significantly larger than post-operative amenorrhea of 40% (95% CI = 27%, 55%; P- I^2 = 85%; heterogeneity < 0.01; 11 studies); (P-interaction comparing the 2 groups < 0.01). The pooled prevalence of pre-operative galactorrhea was 84% (95% CI = 74%, 90%; I^2 = 66.9%; P-heterogeneity < 0.01; 10 studies) and significantly larger than post-operative galactorrhea of 29% (95% CI = 17%, 44%; I^2 = 76.5%; P-heterogeneity < 0.01; 7 studies) (P-interaction < 0.01). Univariate meta-regression on age, continent, publication year, study design, quality, duration, or timing revealed these covariates were not effect modifiers for any of the 3 outcomes (all P > 0.05). No evidence of publication bias was seen using Begg's and Egger's tests (all P > 0.05). Transsphenoidal surgery appeared to improve fertility measures in women with pituitary prolactinomas.

1. Introduction

Pituitary prolactinomas are the most common pathologic cause of elevated prolactin levels and account for 40% of all pituitary tumors. [1–3] These tumors predominantly affect women between the ages of 20–50 and can result in infertility secondary to the effects of hyperprolactinemia on the ovulatory cycle [1,4,5]. Presenting signs and symptoms include galactorrhea, amenorrhea, and infertility [1,4]. Prolactin production is normally under tonic inhibition from dopamine that is produced in the hypothalamus [1], and as such, first-line therapy for prolactinomas is administration of dopamine agonists, such as cabergoline, that act to suppress the production of excess prolactin [1,2]. Success rates with cabergoline treatment are high, resulting in prolactin normalization in over 80% of patients, restoration of ovulation in over 90% of patients, and tumor shrinkage in 70–90% of patients [4,5]; however, for those patients who are unresponsive to pharmacologic therapy, surgical resection of the tumor, most commonly performed via transsphenoidal approach, may be considered [1].

While it is well-established that successful pharmacologic treatment of women with prolactinomas results in resolution of galactorrhea and

Abbreviations: CMA, comprehensive meta-analysis; CI, confidence interval; NOS, Newcastle Ottawa Scale; NA, not applicable; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RE, random-effects; TSS, transsphenoidal surgery

* Corresponding author at: Social and Administrative Sciences, School of Pharmacy, MCPHS University, 179 Longwood Avenue, Boston, MA 02115, USA.
E-mail addresses: rania.mekary@mcphs.edu, Rania.Mekary@bwh.harvard.edu (R.A. Mekary).

[1] Co-first authors.
[2] Co-senior authors.
[3] www.mcphs.edu.

https://doi.org/10.1016/j.clineuro.2018.11.024
Received 26 October 2018; Received in revised form 20 November 2018; Accepted 30 November 2018
Available online 01 December 2018
0303-8467/ © 2018 Published by Elsevier B.V.

restoration of normal menses, [5,6] fertility-related outcomes following surgical resection of prolactinomas have not been consistent. While older studies showed high recurrence rates of prolactinomas following surgical resection, more recent studies have reported remission rates as high as 90%, as well as high success rates for achieving post-operative pregnancy [5,6]; nevertheless, surgery carries an additional risk of hypopituitarism that can itself result in infertility [5]. Moreover, unlike a regimented pharmacologic therapy, outcomes following surgery are influenced by surgeon's experience and hospital volume. [6] Despite the risks inherent to surgery, there is also evidence that pregnancy can lead to progression of prolactinomas [7] and that dopamine agonists might not be safe to continue during pregnancy [5]. Given the potential advantages of surgery over pharmacologic therapy in such situations, [5,7], the efficacy of surgery in terms of fertility-related outcomes should be further explored.

Given the variability on this topic, we performed a meta-analysis to elucidate the efficacy of TSS on fertility outcomes in women with prolactinomas via assessment of post-operative prolactin normalization, as well as rates of resolution of amenorrhea and galactorrhea. To our knowledge, there have been no meta-analyses completed to date to answer this question.

2. Materials and methods

2.1. Eligibility criteria and study selection

To identify studies reporting on outcomes of transsphenoidal surgery (TSS) in women of child-bearing age, a systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. [8] PubMed, Embase, and Cochrane databases were searched through June 13, 2017. Inclusion criteria consisted of any study that described non-pregnant female adult patients ($\geq$18 years of age) with a diagnosis of a prolactinoma who underwent TSS for removal of the prolactinoma. To be included, the study must have had a sample size of at least five subjects and reported on at least one of the following fertility-related outcomes following surgery: patient prolactin levels, menstrual status, and/or presence or absence of galactorrhea. Studies that did not differentiate between patients who received pharmacologic agents prior to surgery versus those who did not, or studies that only included patients treated with pharmacologic agents prior to surgery, were excluded, in order to eliminate the confounding by such pharmacotherapy. Case reports, literature reviews, and systematic reviews were also excluded. Only literature in English was reviewed. The search strategy was developed using the keywords "pituitary neoplasms," "transsphenoidal," "fertility," and related synonyms (Appendix 1 in Supplementary material). After title and abstract screening, remaining articles were read in full-text. Five authors (NL, NN, TS, MA, JA) performed full-text screening and extracted the relevant data. One senior author (HZ) reviewed the included articles and extracted data. Disagreements were resolved by discussion.

2.2. Data extraction and management

The following data were extracted from each study whenever possible: author and year of publication, study design, sample size, patient characteristics (age, tumor size and/or grade, presenting symptoms including amenorrhea/oligomenorrhea, galactorrhea, prolactin levels at presentation, oral contraceptive use), primary treatment (surgery alone or surgery with pharmacologic supplemental therapy), duration of time from diagnosis to TSS, duration of follow-up, and primary and secondary outcomes of the study. Data on surgeon experience and hospital volume were not consistently available across studies and therefore not able to be extracted. When available, information on the following post-surgical outcomes was extracted: any measure of fertility, such as normalization of prolactin levels, return of menses, new pregnancy, and any post-operative complications. When only median data was provided, we converted median to mean and standard deviation following Hozo et al.'s method using IQR range and sample size. [9]

2.3. Bias assessment

Study quality for observational studies was assessed by the New-Castle Ottawa Scale, a scale that assesses studies in three categories, including the (1) selection and (2) comparability of the groups, as well as the (3) assessment of the outcome. [10] This assessment was made by two authors (MA and AJ) independently. Discrepancies were solved by discussion.

2.4. Data analysis

Data analysis was performed using Comprehensive Meta-Analysis (CMA) Version 3 (Biostat, Inc., Englewood, NJ, USA). Pooled effect estimates (pre- and post-operative prevalence or mean difference) using the random-effects (RE) model according to the method of DerSimonian and Laird were calculated for all three outcomes, depending on the available data in the articles. [11] For continuous outcomes (e.g. prolactin levels), units were converted to ng/mL to allow for comparibility across studies. The Cochrane Q test and I-squared values were calculated to assess heterogeneity [12,13]. For this test, a p-value less than 0.1 was considered statistically significant. Univariate meta-regression analysis on age, continent, histological confirmation of the prolactinoma, publication year, study design, quality, duration, and timing was used when possible to assess sources of heterogeneity. Publication bias was assessed with Begg's correlation and Egger's linear regression tests and depicted in Funnel plots. A p-value less than 0.05 was considered significant unless otherwise indicated.

3. Results

The search strategy produced 900 articles after removal of duplicates (Fig. 1). After screening for titles and abstracts, 80 full-texts were reviewed for eligibility. Full-text review resulted in exclusion of 54 articles because the study: (1) included women who did not meet the inclusion criteria, such as those less than 18 years old or having a tumor that was not clearly a pituitary adenoma; (2) was a review or case report; (3) did not involve surgical intervention as part of prolactinoma treatment; or (4) did not contain data on our outcomes of interest.

A total of fourteen 'one group pre-test post-test' design studies with quantitative data were meta-analyzed for at least one of the outcomes (Table 1). [14–27] Seven studies provided data on prolactin values, eleven provided data on pre- and post-operative menstruation, and seven provided data on both pre- and post-operative lactation. Group size ranged between 8 and 120 patients, and patient age ranged between 18 and 56 years. The Newcastle-Ottawa Scale ranged between 4 and 6. Of note, one study contained five patients with primary amenorrhea; these patients were excluded from the amenorrhea analysis [23].

Across all 14 studies, the diagnosis of prolactinoma was based upon a combination of clinical, endocrinologic, radiologic, and in some cases, histopathologic criteria. In 11 of 14 studies, the authors specifically stated that the adenomas were prolactin-secreting tumors, supported by a tissue diagnosis in at least 4 studies. [14,19,24,25] For those tumors that were not histologically confirmed to demonstrate lactotrophs, there is a possibility that the elevated prolactin and resulting clinical symptoms were secondary to a stalk effect from the tumor.

3.1. Prolactin levels

Across the seven studies reporting on pre- and post-prolactin levels, the prolactin levels decreased by an average of 187.7 ng/mL following

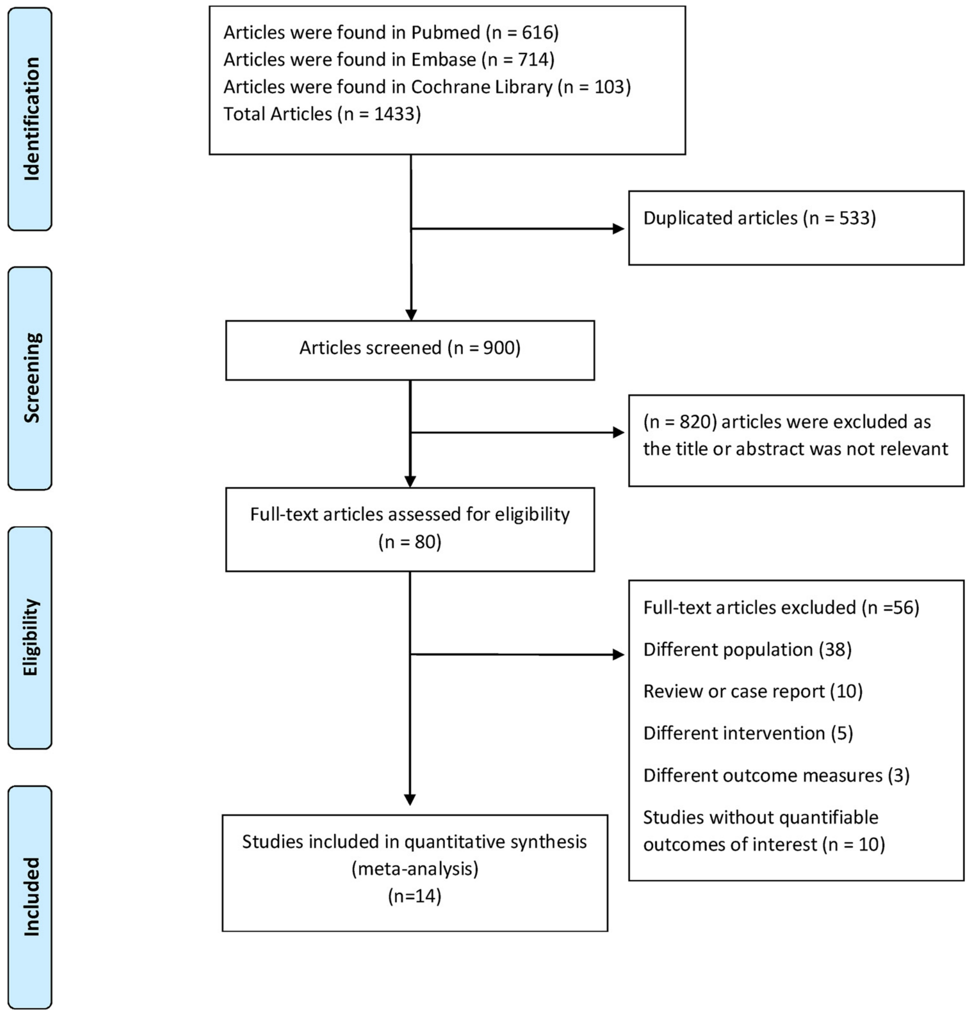

Fig. 1. Study selection process.

surgery. [14,16,18,19,22,24,26] The mean difference of 7 studies in prolactin level between pre- and post-operative was 186.9 (95% CI = 133.7, 240.1) (I^2 = 69.6%; P-heterogeneity < 0.01) (Fig. 2). In other words, the percentage decrease in prolactin levels from pre- to post-surgery ranged between 70.9% and 97.4% with a pooled rate of 80.8% (95% CI = 71.5%, 87.6%) (I^2 = 31.6%; P-heterogeneity = 0.19). A univariate meta-regression model was used to assess for sources of heterogeneity, including age, continent, histological confirmation of the prolactinoma, and study timing, quality, and duration. None of these co-variates was found to explain the differences in results amongst the included studies (all P-interaction > 0.05). Funnel plots of the standard error by the standardized difference in means showed a slight asymmetry to the left of the pooled estimate; however, both Begg's rank correlation test (p = 0.18) and Egger's linear regression test (p = 0.06) indicated no publication bias. After conducting the trim and fill method to correct for any potential publication bias, the recalculated random-effect estimate of 137.9 (95% CI 87.4, 188.5) did not materially change from 186.9 (95% CI = 133.7, 240.1) (Appendix 2 in Supplementary material).

3.2. Amenorrhea/oligomenorrhea

Among 11 studies reporting regularity of menstruation, [15,17–21,23–27] the pooled prevalence of pre-operative amenorrhea was 96% (95% CI = 92%, 98%) (P-heterogeneity = 0.05; I^2 = 45.8%), which was significantly higher than the post-operative amenorrhea of 40% (95% CI = 27%, 55%) (P-heterogeneity < 0.01; I^2 = 85.0%) (P-interaction < 0.01) (Fig. 3). Among the post-operative results, none of the above-mentioned covariates were found to explain the differences in results after performing a univariate meta-regression (All P-interaction > 0.05). The Funnel plot showed no asymmetry (Appendix 3 in Supplementary material); both Begg's rank correlation test (p = 0.70) and Egger's linear regression test (p = 0.18) indicated no publication bias.

3.3. Galactorrhea

Among studies reporting regularity of lactation, [15,17–21,23–27] the pooled prevalence of pre-operative galactorrhea was 84% (95%CI = 74%, 90%) (P-heterogeneity < 0.01; I^2 = 66.9%, 10 studies), which was statistically significantly greater than the post-operative galactorrhea of 29% (95%CI = 17%, 44%) (P-heterogeneity < 0.01; I^2 = 76.5%, 7 studies) (P-interaction < 0.01) (Fig. 4). These results were not materially different when we restricted the analysis to only the 7 studies that reported pre- (80.9%; 95% CI: 75.5%, 86%) and post-operative galactorrhea (21.8%; 95% CI: 25.5%, 28.8%); (P-interaction < 0.001). Among the post-operative results, none of the assessed co-variates was found to explain the differences in results after performing a meta-regression (All P-interaction > 0.05). The Funnel plot showed a slight asymmetry to the right of the pooled estimate; both Begg's rank correlation test (p = 0.88) and Egger's linear regression test (p = 0.58) indicated no publication bias. After conducting the trim and fill method, the recalculated random-effect estimate changed from 29% (95% CI 17%, 44%) to 36.3% (95% CI 21.9%, 38.0%) (Appendix 4 in

Table 1
Characteristics of studies included in the meta-analysis (n = 14).

Study's first author, year, (ref #)	Study Design[1] & Timing	Continent	Sample size undergoing TSS	Age range (years)	Study duration/ length of follow-up, mean, months or years	Amenorrhea (%)	Galactorrhea (%)	Pre-operation prolactin level (mean; ng/mL)	Post-operation prolactin level (mean; ng/mL)	Primary Treatment	NOS[3]
Babey et al. [14]	Retrospective	Europe	24	18-46	2003-2006/ 33.5 months	NA	NA	106.5	2.8	Surgery	6
Chang et al. [15]	Prospective	North America	34	NA	NA/ 6 months	92	96	147.32	NA	Surgery	6
Ciccarelli et al. [16]	Retrospective	Europe	21	19-48	1975-1986/ ≥ 4 years	NA	NA	237.8	12.1	Surgery	6
Faria et al. [17]	Retrospective	North America	100	16-47	1973-1980/ NA	97	84	NA	NA	Surgery	6
Franks et al. [18]	Prospective	Europe	10	23-36	NA	100	30	384.6	78.8	Surgery and bromocriptine	6
Hammond et al. [19]	Retrospective	North America	64	NA	1975-1982/ NA	95	88	365	94.0	Surgery	5
Laws Jr. et al. [20]	Retrospective	Europe	75	20-36	NA	85	80	201.4	NA	Surgery	4
Page et al. [21]	Retrospective	North America	8	25-35	NA/ 11 months	100	100	NA	NA	Surgery and Oral contraceptives	5
Post et al. [22]	Prospective	North America	29	18-50	NA/ 7 weeks	39	NA	166.4	24.0	Surgery	6
Randall et al. [23]	Retrospective	North America	79	18-53	55 months	100	NA	NA	NA	Surgery	6
Rawe et al. [24]	Prospective	North America	30	18-36	18 months	100	93	237.3	39.2	Surgery	6
Saitoh et al. [25]	Retrospective	Asia	79	NA	1975-1984/ NA	100	100	1133.4	NA	Surgery	6
Wiebe et al. [26]	Prospective	North America	14	19-38	1975-1977/ NA	100	71	309.6	90.0	Surgery	6
Woosley et al. [27]	Retrospective	North America	36	18-56	1977-1980/ NA	100	77	NA	NA	Surgery	6

[1]The design of these studies was one group pre-test post-test design.
[2]NOS = Newcastle Ottawa Scale.
[3]NA = not applicable.

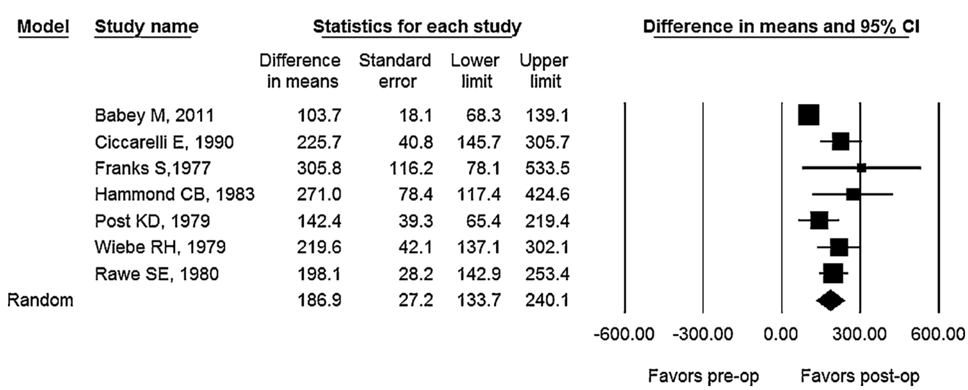

Fig. 2. Pooled mean difference for 7 studies in pre-operative vs. post-operative prolactin levels relative to surgery. Horizontal lines denote 95% CIs, solid squares represent the point estimate of each study and the diamond represents the pooled estimate of the intervention effect. I^2 = 69.6%, P-heterogeneity < 0.01, 7 studies.

Supplementary material).

3.4. Complications

Due to the heterogeneity in reporting across studies, we were unable to perform a meta-analysis on the complications following prolactinoma surgery. However, we have presented the data available on complications in Table 2. Overall, there were no deaths and minimal morbidity. The most common complication included diabetes insipidus, with rates ranging from 4 to 87% in studies reporting on this outcome. Rates of post-operative hypopituitarism ranged from 0 to 23%, although only two studies [16,17] had rates greater than 10%. Additional, rare complications are presented in Table 2.

4. Discussion

The present study demonstrated that in women with prolactin-secreting pituitary adenomas, it is possible to restore fertility via transsphenoidal surgery. By pooling the results of fourteen observational studies, we demonstrated that transsphenoidal surgery resulted in a significant decrease in prolactin levels, as well as a significant decrease in the prevalence of both amenorrhea and galactorrhea. These results were consistent with our hypothesis that transsphenoidal surgery would be an effective means by which to restore fertility in women of child-

Clinical Neurology and Neurosurgery 176 (2019) 53–60

Model	Group by Operation	Study name	Statistics for each study		
			Event rate	Lower limit	Upper limit
	a-Pre Op	Chang RJ, 1977	0.92	0.73	0.98
	a-Pre Op	Faria M, 1982	0.97	0.91	0.99
	a-Pre Op	Franks S, 1977	0.95	0.55	1.00
	a-Pre Op	Hammond CB, 1983	0.95	0.86	0.98
	a-Pre Op	Laws Jr ER, 1982	0.85	0.75	0.92
	a-Pre Op	Page LK, 1979	0.94	0.50	1.00
	a-Pre Op	Saitoh Y, 1986	0.99	0.91	1.00
	a-Pre Op	Wiebe RH, 1979	0.97	0.63	1.00
	a-Pre Op	Woosley RE, 1982	0.99	0.82	1.00
	a-Pre Op	Randall RV, 1983	0.99	0.91	1.00
	a-Pre Op	Rawe,S. E., 1980	0.98	0.79	1.00
Random	a-Pre Op		0.96	0.92	0.98
	b-Post Op	Chang RJ, 1977.	0.28	0.14	0.48
	b-Post Op	Faria M, 1982.	0.33	0.25	0.43
	b-Post Op	Franks S, 1977.	0.40	0.16	0.70
	b-Post Op	Hammond CB, 1983.	0.98	0.90	1.00
	b-Post Op	Laws Jr ER, 1982.	0.04	0.01	0.12
	b-Post Op	Page LK, 1979.	0.25	0.06	0.62
	b-Post Op	Saitoh Y, 1986.	0.56	0.45	0.66
	b-Post Op	Wiebe RH, 1979.	0.57	0.32	0.79
	b-Post Op	Woosley RE, 1982.	0.64	0.47	0.78
	b-Post Op	Randall RV, 1983.	0.24	0.16	0.35
	b-Post Op	Rawe,S. E., 1980.	0.33	0.19	0.52
Random	b-Post Op		0.40	0.27	0.55
Random	Overall		0.71	0.60	0.80

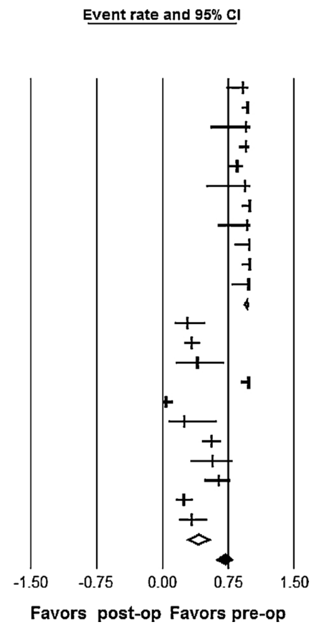

Fig. 3. Menstruation outcome comparing pre-operative prevalence of amenorrhea and post-operative prevalence of amenorrhea across 11 studies. Pooled pre-operative prevalence = 96%; 95% CI: 92%, 98%; I^2 = 45.8%; p-heterogeneity = 0.09; and pooled post-operative prevalence = 40%; 95% CI: 27%, 55%; I^2 = 85.0%; P-heterogeneity < 0.01; (p-interaction < 0.01).

bearing age who suffer from amenorrhea and galactorrhea secondary to a prolactinoma.

Elevated prolactin is an important cause of infertility in women of child-bearing age, accounting for 15–20 percent of patients with amenorrhea. [18] The greatest causative agent of hyperprolactinemia is a prolactinoma [18]. Prolactinomas are typically managed conservatively with pharmacologic therapy, but can be more aggressively treated with surgery in certain situations [14].

To our knowledge, no meta-analyses have yet been completed to determine the impact of transsphenoidal surgery in restoring fertility in women with pituitary adenomas. The current guidelines for the treatment of prolactinomas recommend medical treatment with a dopamine agonist, such as cabergoline or bromocriptine, allowing for restoration of normal prolactin levels in 75–90% of patients. [28] Indications for surgical resection of prolactinomas include failure of pharmacologic therapy, growth of the tumor size despite the use of dopamine agonist, or pituitary apoplexy [28]. While several studies have been published to describe the specific effects of transsphenoidal surgery on fertility in women with prolactinomas, there is little consensus on the extent of impact that surgery has on restoration of fertility in these women.

Multiple studies have demonstrated a restoration to normal or near-normal prolactin levels following transsphenoidal surgery, with decreases ranging from 142.4 to 305.8 ng/mL between pre- and post-operative prolactin levels [14,16,18,19,22,26]. Our mean difference of 187.7 ng/mL reported here is therefore consistent with the published literature. In one previously published cohort study, Babey et al. further divided patients into two groups based on size of the prolactinoma, categorizing microprolactinomas as 1–10 mm and macro-prolactinomas as 11–20 mm. After such stratification, they demonstrated that both size of the adenoma and pre-operative prolactin levels were correlated with remission rates; specifically, the study found that patients with microprolactinomas had markedly lower levels of pre-operative prolactin levels compared to patients with macro-prolactinomas, and were also significantly more likely to achieve long-term remission [14]. Due to the heterogeneity in available data across the studies in our analysis, we were unable to study correlations between size of tumor and pre-operative prolactin levels. Nevertheless, our results showing a significant decrease between pre- and post-operative prolactin levels are consistent with the aforementioned published studies, although further work is needed to assess the association between tumor size and prolactin

Model	Group by Operation	Study name	Statistics for each study		
			Event rate	Lower limit	Upper limit
	a-Pre Op	Chang RJ, 1977	0.96	0.76	0.99
	a-Pre Op	Faria M, 1982	0.84	0.75	0.90
	a-Pre Op	Franks S, 1977	0.30	0.10	0.62
	a-Pre Op	Hammond CB, 1983	0.88	0.77	0.94
	a-Pre Op	Laws Jr ER, 1982	0.80	0.69	0.88
	a-Pre Op	Page LK, 1979	0.94	0.50	1.00
	a-Pre Op	Saitoh Y, 1986	0.99	0.91	1.00
	a-Pre Op	Wiebe RH, 1979	0.71	0.44	0.89
	a-Pre Op	Woosley RE, 1982	0.78	0.61	0.88
	a-Pre Op	Rawe,S. E., 1980	0.93	0.77	0.98
Random	a-Pre Op		0.84	0.74	0.90
	b-Post Op	Chang RJ, 1977.	0.08	0.02	0.27
	b-Post Op	Faria M, 1982.	0.27	0.19	0.37
	b-Post Op	Franks S, 1977.	0.20	0.05	0.54
	b-Post Op	Page LK, 1979.	0.25	0.06	0.62
	b-Post Op	Wiebe RH, 1979.	0.43	0.21	0.68
	b-Post Op	Woosley RE, 1982.	0.64	0.47	0.78
	b-Post Op	Rawe,S. E., 1980.	0.17	0.07	0.34
Random	b-Post Op		0.29	0.17	0.44
Random	Overall		0.63	0.51	0.73

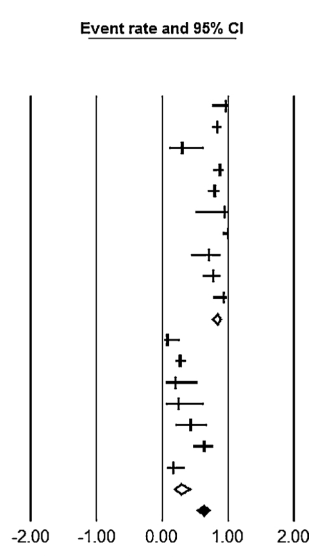

Fig. 4. Galactorrhea outcome comparing pre-operative prevalence of galactorrhea and post-operative prevalence of galactorrhea across 10 and 7 studies, respectively. Pooled pre-operative prevalence = 84%; 95% CI: 74%, 90%; I^2 = 66.9%; p-heterogeneity < 0.01, 10 studies; vs. pooled post-operative prevalence = 29%; 95% CI: 17%, 44%; I^2 = 76.5%; p-heterogeneity < 0.01, 7 studies; (p-interaction < 0.01).

Table 2
Incidence of Complications following Surgery for Prolactinomas.

Study's first author, year, (ref #)	Sample size undergoing TSS	Rates of post-operative hypopituitarism, no. of patients (%)	Diabetes insipidus, no. of patients (%)	Additional complications, no. of patients (%)	Major complications and mortality rate
Babey et al. [14]	24	1 (4), permanent hypogonadotrophic hypogonadism	1 (4), transient DI	N/R	None
Chang et al. [15]	34	1(3), panhypopituitarism	10 (29)	2(6), SIADH; 2(6), CSF leak; 2(6), bleeding; 1(3), meningitis	None
Ciccarelli et al. [16]	21	5 (23)[a]	5 (23), normalized in 4[a]	N/R	N/R
Faria et al. [17]	100	15 (23): 2 with deficits in multiple axes, 13 with deficits in one axis only; only 2/15 required long-term replacement[b]	60 (60), transient DI; 3 (3) with permanent DI	1(1), CSF rhinorrhea; 1 1(1), maxillary sinusitis; 3(3), superficial abdominal wound infections	None
Franks et al. [18]	10	1 (10); panhypopituitarism	N/R	N/R	N/R
Hammond et al. [19]	64	None	Transient DI in many patients; cleared in all except 2 prior to discharge (and at 6 and 15 weeks in these 2)	N/R	None
Laws Jr. et al. [20]	75	N/R	N/R	N/R	N/R
Page et al. [21]	8	No post-operative hormonal supplements needed in any of the patients	3 (37.5), mild DI	No CSF leaks or infections	None
Post et al. [22]	29	1 (3), severe postoperative hormonal deficiencies[s]	Exact incidence not reported	1(3), proptosis that self-resolved; 2(7), CSF leakage; 3(10), nasal septal perforation; 1(3), minor fracture of maxilla[c]	None
Randall et al. [23]	79	No thyroid or adrenal insufficiency after the operation	9 (9), transient DI[d]	1(1), visual field deficit	None
Rawe et al. [24]	30	Microadenoma group (n = 21): no significant change in pituitary function after surgery; macroadenoma group (n = 9): 2 (22) patients with hypopituitarism pre-operatively and on replacement after surgery	26 (87), transient DI	3(10), CSF rhinorrhea (all resolved)	None
Saitoh et al. [25]	79	Overall increase in anterior pituitary dysfunction from pre- to post-operative[e]	Transient polyuria in most patients	None	None
Wiebe et al. [26]	14	TSH, GH, thyroxine, LH, FSH, plasma cortisol, and/or urinary 17-hydroxycorticosteroid hormones normal in all patients post-operatively.	4 (29), transient DI	None	None
Woosley et al. [27]	36	3 (8), transient low cortisol[a]	9 (24), transient DI[a]	2(5), transient R arm weakness; 2(5), monilia of mouth; 2(5), herpes of lip; 2(5), CSF leak; 1(3), R maxillary sinusitis; 1(3), pharyngitis; 1(3), transient proptosis; 1(3), ventricular tachycardia; 1(3), bleeding[a]	None

CSF = cerebrospinal fluid; DI = diabetes insipidus; FSH = follicle-stimulating hormone; GH = growth hormone LH = lutenizing hormone; N/R = not reported; TSH = thyroid-stimulating hormone. [a]Data on complications not stratified by males and females, so rates here represent entire cohort, not just females; [b]35 patients had pituitary dysfunction prior to surgery; [c]Complication rates only available for all 30 patients (entire cohort), while our meta-analysis excluded one patient on basis of age; [d]DI rates only available for all 100 patients (entire cohort), which included males and females; [e]raw percentages only reported in macroprolactinoma and macroprolactinoma groups, but not as overall percentages.

normalization.

Prior work has also shown improvement in galactorrhea and resolution of amenorrhea in women following resection of prolactinomas. Specifically, previously reported rates of menstrual restoration following surgery have ranged from 43 to 94% [26,15,25,21,27]. Similarly high rates of galactorrhea resolution have also been reported, ranging from 57 to 100% [26,15,21,27]. The results from our present analysis, which demonstrate a pre-operative to post-operative improvement rate of 56% for amenorrhea and 55% for galactorrhea, are on the lower range compared to the aforementioned studies, but nevertheless demonstrate a robust and significant improvement in symptoms following surgery.

Whether the resolution of symptoms is affected by the degree of prolactin elevation has also been previously reported on. Studies of women with amenorrhea-galactorrhea syndrome associated with a prolactinoma have demonstrated a marked difference in response to transsphenoidal surgery depending on patients' pre-operative prolactin levels [17,29]. Specifically, these studies have found that patients with pre-operative prolactin levels less than 200 ng/mL were more likely to experience resolution of both amenorrhea and galactorrhea following surgery as compared to those with prolactin levels greater than 200 ng/mL [17,29]. While we were unable to study the effect of degree of pre-operative prolactin elevation on response to surgery, this appears to be a well-described phenomenon that warrants clinical attention. Specifically, patients with prolactinomas with a prolactin level below 200 ng/mL may make better surgical candidates due to the anticipated degree of response compared to those with pre-operative prolactin levels above 200 ng/mL.

In addition to pre-operative prolactin levels, there are a number of other factors that may influence response to surgery and risk for relapse, including extrasellar tumor extension [30], tumor size [31,32], patient age [31,32], and gender [32]. Interestingly, in a large meta-analysis that pooled outcomes from over 3,000 patients with prolactinomas in order to better assess factors associated with prolactinoma recurrence, the authors found that tumor size, tumor invasion, age, and gender, were not significant factors for recurrence [33]. However, they did find that a low basal prolactin level following surgery, as well as normalization of the TRH test, were favorable factors associated with permanent cure [33]. Further study of these factors in prospective trials may be warranted, and each should be considered and discussed with patients prior to surgery in order to risk-stratify, optimize management, and prepare patients for the response they may expect following an operation.

While the exact pathogenesis of prolactinomas remains unclear, the goal of treatment is to normalize serum prolactin levels and improve endocrine symptoms, restore infertility. and improve sexual dysfunction [34]. It is thought that elevated prolactin causes gonadal disturbances by both direct inhibition of steroidogenesis, as well as via suppression of the pulsatile release of gonadotropin-releasing hormone secretion [35]. This ultimately presents as menstrual irregularities in women and can cause infertility. Surgical resection of the prolactin-producing tumor allows for removal of the source of prolactin and, as demonstrated in our analysis, results in a significant decrease in serum prolactin levels. The return of menses observed across the patients in our pooled analysis is therefore likely secondary to the decrease in prolactin and subsequent release of inhibition on the gonadal axis. While it is known that space-occupying tumors that impinge on the pituitary gland may cause underlying damage to normal pituitary tissue [36], the results of our study suggest that the gonadal dysfunction caused by prolactinomas is a transient phenomenon that can typically be expected to improve with removal of tumor.

The results of our analysis demonstrate the effectiveness of surgery in decreasing prolactin and restoring fertility in women with prolactinomas; however, these potential benefits should still be weighed against the risks of surgery for each patient. Overall, across all studies, there was no mortality and minimal morbidity observed following surgery. Despite the high prevalence of post-operative diabetes insipidus, in almost all cases, this was transient and resolved within a short period of time. Moreover, except for two studies, [16,17] anterior pituitary function was preserved in > 90% of all patients after prolactinoma resection. Of note, in one of these two studies, only two of the fifteen patients with pituitary dysfunction following surgery actually required long-term replacement therapy. Therefore, while it is essential for surgeons to communicate with patients about the potential for pituitary dysfunction and other complications following surgery, the risk appears to be relatively low."

4.1. Limitations and strengths

A major limitation of this meta-analysis was the lack of comparable data on direct fertility outcomes, such as rates of pregnancy or time to conception; while some of the studies did provide data on what percentage of their patients successfully conceived following prolactinoma surgery, a number of factors made this information challenging to interpret. For example, it was unclear whether all participants in the studies were even attempting conception at the time of the study, and it is possible that with longer follow-up times, there would be a substantial increase in the number of patients who succeeded in conceiving. Moreover, some patients may have been utilizing contraception following surgery, thereby confounding the use of conception as a measurement of restored fertility. Overall, given the heterogeneity across studies in if, how, and across what time periods pregnancy rates were measured, we were unable to include this particular outcome in our meta-analysis. While having this more direct data on fertility would have strengthened our meta-analysis, most patients with hyperprolactinemia will require normalization of prolactin levels, as well as a return of ovulatory cycles, in order to achieve a successful pregnancy; hence, this justifies the use of a decrease in prolactin, resolution of galactorrhea, and/or resumption of menses as proxies for restoration of fertility.

Another limitation of the study was the heterogeneity in patient follow-up times within the same study. For example, Wiebe et al. reported a wide follow-up range of six months to three years in their study [26]. This is particularly important for our endpoints, because prior research has demonstrated that recurrence of prolactinemia is frequent but delayed [37]. Serri et al. found a 50% recurrence rate in patients with micro-prolactinomas at a mean of 4 years after surgery and an 80% recurrence rate in patients with macro-prolactinomas at a mean of 2.5 years after surgery [37]. It is therefore possible that some of the studies in our analysis, due to their shorter follow-up times, may have underestimated the true rate of recurrence. Nevertheless, study duration did not appear to alter our results according to the meta-regression analysis. An additional limitation of this study was that we may have been unable to fully account for additional factors that were causing infertility in the patient population. For example, Hammond et al. reported on one woman with a prolactinoma who was later found to have tubal disease as the cause of her infertility [19]. There may have been other patients in the included studies who had similar such issues as the cause of their infertility, but who had not been previously diagnosed. As factors independent of the prolactinomas may have been the cause of infertility in such patients, this may have resulted in an underestimation of the fertility benefits from surgery in our analysis. Finally, it has been reported that the chronic use of oral contraceptives (OCPs) may cause an increase in prolactin and lead to amenorrhea [21]. We were unable to account for the potential effect of OCP use on fertility outcomes as information was not consistently reported across the included studies.

Despite these limitations, this meta-analysis based on observational studies evaluated multiple outcomes after extensive review of the literature. To our knowledge, this is the first meta-analysis on this topic. Furthermore, statistically significant decreases in serum prolactin levels and in rates of amenorrhea and galactorrhea following TSS for prolactinomas were identified. Another strength of this study was that we examined pre- and post-operative levels of prolactin, as well as return of menstruation following surgery. This was essential as studies have shown that normal menstruation and fertility may be restored following surgical removal of a prolactinoma even when post-operative prolactin levels are not reduced [17]. Similarly, women can remain amenorrheic even with normal post-operative prolactin levels [17]. It was therefore important to consider both endpoints, as one may not necessarily correlate with the other [17]. In our study, we found that TSS resulted in both a significant decrease in prolactin, as well as return of menses.

5. Conclusions

This meta-analysis suggested that transsphenoidal surgery resulted in robust responses in patients with prolactinomas, decreasing prolactin levels and rates of both amenorrhea and galactorrhea, thus allowing for improvements in fertility.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

We have no acknowledgments.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2018.11.024.

References

[1] A. Wong, J.A. Eloy, W.T. Couldwell, J.K. Liu, Update on prolactinomas. Part 1: clinical manifestations and diagnostic challenges, J. Clin. Neurosci. 22 (10) (2015) 1562–1567.
[2] E. Bloomgarden, M.E. Molitch, Surgical treatment of prolactinomas: cons, Endocrine 47 (3) (2014) 730–733.
[3] A. Glezer, M.D. Bronstein, Prolactinomas, Endocrinol. Metab. Clin. North Am. 44 (1) (2015) 71–78.
[4] L. Vroonen, M.L. Jaffrain-Rea, P. Petrossians, G. Tamagno, P. Chanson, L. Vilar, F. Borson-Chazot, L.A. Naves, T. Brue, B. Gatta, B. Delemer, E. Ciccarelli, P. Beck-Peccoz, P. Caron, A.F. Daly, A. Beckers, Prolactinomas resistant to standard doses of cabergoline: a multicenter study of 92 patients, Eur. J. Endocrinol. 167 (5) (2012) 651–662.
[5] W.C. Jean, D.R. Felbaum, Fertility, pregnancy, and prolactinoma: a survey of pituitary surgeons' view and review of the literature, J. Clin. Neurosci. 42 (2017) 198–203.
[6] A. Faje, L. Nachtigall, Current treatment options for hyperprolactinemia, Expert Opin. Pharmacother. 14 (12) (2013) 1611–1625.
[7] R.W. Griffith, I. Turkalj, P. Braun, Pituitary tumours during pregnancy in mothers treated with bromocriptine, Br. J. Clin. Pharmacol. 7 (4) (1979) 393–396.
[8] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009) e1000097.
[9] S.P. Hozo, B. Djulbegovic, I. Hozo, Estimating the mean and variance from the median, range, and the size of a sample, BMC Med. Res. Methodol. 5 (2005) 13.
[10] G.A. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-analyses, (2014) http//www.ohrica/programs/clinical_epidemiology/oxfordhtm. (Accessed June 10, 2018).
[11] R. DerSimonian, N. Laird, Meta-analysis in clinical trials, Control. Clin. Trials 7 (3) (1986) 177–188.
[12] T.B. Huedo-Medina, J. Sanchez-Meca, F. Marin-Martinez, J. Botella, Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol. Methods 11 (2) (2006) 193–206.
[13] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (11) (2002) 1539–1558.
[14] M. Babey, R. Sahli, I. Vajtai, R.H. Andres, R.W. Seiler, Pituitary surgery for small prolactinomas as an alternative to treatment with dopamine agonists, Pituitary 14 (3) (2011) 222–230.
[15] R.J. Chang, W.R. Keye Jr., J.R. Young, C.B. Wilson, R.B. Jaffe, Detection, evaluation, and treatment of pituitary microadenomas in patients with galactorrhea and amenorrhea, Am. J. Obstet. Gynecol. 128 (4) (1977) 356–363.
[16] E. Ciccarelli, E. Ghigo, C. Miola, G. Gandini, E.E. Muller, F. Camanni, Long-term follow-up of' cured' prolactinoma patients after successful adenomectomy, Clin. Endocrinol. (Oxf) 32 (5) (1990) 583–592.
[17] M.A. Faria Jr., G.T. Tindall, Transsphenoidal microsurgery for prolactin-secreting pituitary adenomas, J. Neurosurg. 56 (1) (1982) 33–43.
[18] S. Franks, H.S. Jacobs, M.G. Hull, S.J. Steele, J.D. Nabarro, Management of hyperprolactinaemic amenorrhoea, Br. J. Obstet. Gynaecol. 84 (4) (1977) 241–253.
[19] C.B. Hammond, A.F. Haney, M.R. Land, J.V. van der Merwe, S.J. Ory, R.H. Wiebe, The outcome of pregnancy in patients with treated and untreated prolactin-secreting pituitary tumors, Am. J. Obstet. Gynecol. 147 (2) (1983) 148–157.
[20] E.R. Laws Jr., N.C. Fode, R.V. Randall, C.F. Abboud, C.B. Coulam, Pregnancy after transsphenoidal surgery for pituitary microadenoma, Neuro-endocrinol. Lett. 4 (3) (1982) 195.
[21] L.K. Page, W.J. LeMaire, Prolactin-producing pituitary adenomas, J. Microsurg. 1 (3) (1979) 182–186.
[22] K.D. Post, B.J. Biller, L.S. Adelman, M.E. Molitch, S.M. Wolpert, S. Reichlin, Selective transsphenoidal adenomectomy in women with galactorrhea-amenorrhea, JAMA 242 (2) (1979) 158–162.
[23] R.V. Randall, E.R. Laws Jr., C.F. Abboud, M.J. Ebersold, P.C. Kao, B.W. Scheithauer, Transsphenoidal microsurgical treatment of prolactin-producing pituitary adenomas. Results in 100 patients, Mayo Clin. Proc. 58 (2) (1983) 108–121.
[24] S.E. Rawe, H.O. Williamson, J.H. Levine, S.A. Phansey, D. Hungerford, W.Y. Adkins, Prolactinomas: surgical therapy, indications and results, Surg. Neurol. 14 (3) (1980) 161–167.
[25] Y. Saitoh, S. Mori, N. Arita, M. Nagatani, T. Hayakawa, K. Koizumi, O. Tanizawa, T. Uozumi, H. Mogami, Treatment of prolactinoma based on the results of transsphenoidal operations, Surg. Neurol. 26 (4) (1986) 338–344.
[26] R.H. Wiebe, R.S. Kramer, C.B. Hammond, Surgical treatment of prolactin-secreting microadenomas, Am. J. Obstet. Gynecol. 134 (1) (1979) 49–55.
[27] R.E. Woosley, J.S. King, L. Talbert, Prolactin-secreting pituitary adenomas: neurosurgical management of 37 patients, Fertil. Steril. 37 (1) (1982) 54–60.
[28] A. Rogers, N. Karavitaki, J.A. Wass, Diagnosis and management of prolactinomas and non-functioning pituitary adenomas, BMJ 349 (2014) g5390.
[29] J.N. Domingue, I.L. Richmond, C.B. Wilson, Results of surgery in 114 patients with prolactin-secreting pituitary adenomas, Am. J. Obstet. Gynecol. 137 (1) (1980) 102–108.
[30] M. Losa, P. Mortini, R. Barzaghi, L. Gioia, M. Giovanelli, Surgical treatment of prolactin-secreting pituitary adenomas: early results and long-term outcome, J. Clin. Endocrinol. Metab. 87 (7) (2002) 3180–3186.
[31] P.B. Nelson, M. Goodman, J.C. Maroon, A.J. Martinez, J. Moossy, A.G. Robinson, Factors in predicting outcome from operation in patients with prolactin-secreting pituitary adenomas, Neurosurgery 13 (6) (1983) 634–641.
[32] G. Raverot, A. Wierinckx, E. Dantony, C. Auger, G. Chapas, L. Villeneuve, T. Brue, D. Figarella-Branger, P. Roy, E. Jouanneau, M. Jan, J. Lachuer, J. Trouillas, Hypopronos, Prognostic factors in prolactin pituitary tumors: clinical, histological, and molecular data from a series of 94 patients with a long postoperative follow-up, J. Clin. Endocrinol. Metab. 95 (4) (2010) 1708–1716.
[33] F. Roelfsema, N.R. Biermasz, A.M. Pereira, Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis, Pituitary 15 (1) (2012) 71–83.
[34] Z. Yan, Y. Wang, X. Shou, J. Su, L. Lang, Effect of transsphenoidal surgery and standard care on fertility related indicators of patients with prolactinomas during child-bearing period, Int. J. Clin. Exp. Med. 8 (11) (2015) 21557–21564.
[35] P. Crosignani, Management of hyperprolactinemic infertility, Middle East Fertil. Soc. J. 17 (2) (2012) 63–69.
[36] S.Y. Kim, Diagnosis and treatment of hypopituitarism, Endocrinol. Metab. (Seoul) 30 (4) (2015) 443–455.
[37] O. Serri, E. Rasio, H. Beauregard, J. Hardy, M. Somma, Recurrence of hyperprolactinemia after selective transsphenoidal adenomectomy in women with prolactinoma, N. Engl. J. Med. 309 (5) (1983) 280–283.