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Late Effects of Parasellar Lesion Treatment: Hypogonadism and Infertility

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Abstract
Central hypogonadism, also defined as hypogonadotropic hypogonadism, is a recognized complication of hypothalamic-pituitary-gonadal axis damage following treatment of sellar and parasellar masses. In addition to radiotherapy and surgery, CTLA4-blocking antibodies and alkylating agents such as temozolomide can also lead to hypogonadism, through different mechanisms. Central hypogonadism in boys and girls may lead to pubertal delay or arrest, impairing full development of the genitalia and secondary sexual characteristics. Alternatively, cranial irradiation or ectopic hormone production may instead cause early puberty, affecting hypothalamic control of the gonadostat. Given the reproductive risks, discussion of fertility preservation options and referral to reproductive specialists before treatment is essential. Steroid hormone replacement can interfere with other replacement therapies and may require specific dose adjustments. Adequate gonadotropin stimulation therapy may enable patients to restore gametogenesis and conceive spontaneously. When assisted reproductive technology is needed, protocols must be tailored to account for possible long-term gonadotropin insufficiency prior to stimulation. The aim of this review was to provide an overview of the risk factors for hypogonadism and infertility in patients treated for parasellar lesions and to give a summary of the current recommendations for management and follow-up of these dysfunctions in such patients. We have also briefly summarized evidence on the physiological role of pituitary hormones during pregnancy, focusing on the management of pituitary deficiencies.

Introduction

The parasellar region is a highly complex and fragile area without any strong anatomic boundaries. It comprises structures and spaces surrounding the sella turcica, namely the suprasellar cistern, the cavernous sinus, the hypothalamus and the third ventricle [1, 2]. In the long term, patients with a parasellar lesion are likely to develop endocrine disorders, resulting from either the tumorous

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or infiltrative process itself or its treatments, which can have both local and distal side effects. Masses occupying the parasellar region are normally due to a pituitary adenoma extending from the sella. Less frequently, they may arise from a primary parasellar tumour or a non-tumorous cystic lesion [1]. The most common malignant lesions occupying the parasellar region are gliomas, followed by germ cell tumours, primary lymphomas and metastases. Other potentially malignant tumours include craniopharyngiomas, chordomas, chondrosarcomas, haemangiopericytomas and Langerhans cell histiocytosis, while benign tumours include meningiomas, epidermoid cysts, dermoid cysts and Rathke cysts [2].

The diagnostic approach to a suspected suprasellar/parasellar lesion should start with radiological imaging. Computed tomography scans are generally considered to offer the most information, as they enable an accurate assessment of bony details and calcifications. However, magnetic resonance imaging is the imaging technique of choice, as it produces multiplanar high-contrast images, while more recent advanced magnetic resonance imaging techniques such as diffusion-weighted imaging and perfusion-weighted imaging [3–5] can better define the morphological characteristics of the lesion. ^{18}F-fluoro-deoxyglucose and ^{68}Ga-positron emission tomography can be used for functional imaging, but only in specific tumour settings [6, 7].

The second diagnostic step is a complete pre-treatment evaluation of hormone deficiencies, to help establish the prognosis and initiate a suitable therapy. A complete description of the tests used to investigate the hypothalamic-pituitary axis in men and women was previously provided [8–11]; a brief summary is reported in Table 1.

Parasellar Lesions: The Effects of Treatment

The remarkable improvement in the survival of children and adults diagnosed with cancer and the high incidence of chronic disorders in adult survivors of childhood cancer highlight the importance of recognizing factors predictive of and responsible for future morbidities [12]. Changes in hypothalamic, pituitary and peripheral gland function are frequently described in childhood cancer survivors [13–15]. Recognition of such changes is particularly important given their association with impaired growth, pubertal development and reproductive function, decreased bone mineral density, a higher prevalence of infectious diseases, and poor quality of life [16–18]. The endocrine risks associated with the various treatments for parasellar lesions are described in Table 2.

For slow-growing lesions, surgery to remove as much of the mass as possible is generally the first treatment choice. Radiotherapy is generally used to prevent recurrences. Primary or adjuvant medical therapy and radiotherapy may be an option for highly recurrent or particularly aggressive lesions, as well as for lesions at risk of becoming malignant. In the management of these patients, it is essential to minimize the undesirable effects of the treatments, promptly diagnose any hormone deficiencies [19, 20] and initiate hormone replacement therapy (HRT), where indicated [21–25]. Central hypogonadism, also known as hypogonadotropic hypogonadism (HH), may occur after surgery, cranial irradiation of parasellar tumours such as craniopharyngioma or germinoma, or hypothalamic-pituitary diseases, such as in patients with glioma. Overall, the incidence of HH amongst childhood cancer survivors has been reported as 6.3% [26].

The risk of infertility in adults depends on complex interactions between the characteristics of the tumour (histology, proximity to the hypothalamus), the individual patient (age, sex, genetic predisposition, pre-existing polycystic ovary syndrome in females) and the treatment (radiation, high-dose chemotherapy, especially with alkylating agents, immunotherapies, high-dose glucocorticoids) [27–29].

Radiotherapy and Its Effects on the Hypothalamic-Pituitary-Gonadal Axis

In recent decades, the survival rates following a childhood brain tumour have increased to 75%. This has raised interest in the undesirable effects of its treatments [30]. Radiation-induced anterior pituitary hormone deficiency is the most common irreversible long-term complication of cancer treatment. It is now estimated that up to 50% of treated childhood cancer survivors will eventually develop an endocrinopathy. Strict follow-up is required to minimize the detrimental effects of the treatment on growth, bone density, pubertal development, fertility and quality of life [13]. The neurotoxicity induced by radiotherapy depends on the total dose, the fraction size and the duration of the radiation programme [31–34].

Significant improvements in imaging techniques and radiotherapy technology have enabled more precise, accurate and focal irradiation with fewer side effects. Radiation techniques for patients with sellar/parasellar lesions have evolved from 3D conformal radiotherapy to

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Table 1. Summary of tests used to investigate the HPG axis in men and women to rule out primary and secondary hypogonadism

Test	Males			Females		
	primary hypogonadism (gonadal failure following chemotherapy or radiotherapy)	secondary hypogonadism (acquired hypothalamic defect)	secondary hypogonadism (acquired hypopituitarism/ acquired isolated gonadotropic deficiency)	primary hypogonadism (gonadal failure following chemotherapy or radiotherapy)	secondary hypogonadism (acquired hypothalamic defect)	secondary hypogonadism (acquired hypopituitarism/ acquired isolated gonadotropic deficiency)
Baseline examinations to evaluate HPG axis function	LH, FSH, total T, SHBG, inhibin B, albumin	LH, FSH, total T, SHBG, inhibin B, albumin	LH, FSH, total T, SHBG, inhibin B, albumin	LH, FSH, oestradiol, PRL, inhibin B, AMH (in pre-menopausal women only, as a marker of ovarian reserve)	LH, FSH, oestradiol, PRL, inhibin B, AMH (in pre-menopausal women only, as a marker of ovarian reserve)	LH, FSH, oestradiol, PRL, inhibin B, AMH (in pre-menopausal women only, as a marker of ovarian reserve)
Expected baseline examination results	Usually high LH, high FSH, low T, low inhibin B	Usually normal/low LH, normal/low FSH, low T, low inhibin B	Usually normal/low LH, normal/ low FSH, low T, low inhibin B	Usually high FSH, normal/high LH, low oestradiol, normal PRL, low AMH	Usually normal/low LH, normal/low FSH, low oestradiol, normal PRL, low inhibin B, normal/low AMH	Usually normal/low LH, normal/ low FSH, low oestradiol, normal PRL, low inhibin B, normal/low AMH
Dynamic tests to evaluate HPG axis function and expected results						
Expected GnRH test results	Not indicated	Potentially excessive LH response if recent, or a reduced response if longstanding; if longstanding, priming with repeated doses of GnRH may induce a normal response	Reduced response; a 36-h priming with GnRH is suggested prior to the classic GnRH test; after GnRH priming, the LH increment is 5 times lower than normal; ratio of the maximum delta of FSH/LH >0.55	Not indicated	Usually normal or reduced LH and FSH response; priming with GnRH is suggested prior to the classic GnRH test in cases of reduced LH and FSH response	Usually normal or reduced response of LH and FSH pulses; most patients with low LH and FSH baseline values show a minimal response to GnRH; priming with GnRH is suggested prior to the classic GnRH test in cases of reduced LH and FSH response
Expected HCG test results	Not indicated	With recent hypothalamic dysfunction and in post-pubertal boys, T may increase normally[1]; T does not increase to normal[1] range in pre-pubertal boys	Normal T response: 2- to 3-fold increase in T if disease presented in adulthood; T does not rise normally in prepubertal hypogonadism	Not indicated	Not indicated	Not indicated
Expected clomiphene test results	Not indicated	Lack of LH and FSH response; second choice among dynamic HPG axis tests	Lack of LH and FSH response; second choice among dynamic HPG axis tests	Not indicated	Reduced or no LH, FSH, and oestradiol response; occasionally used to evaluate dynamic HPG axis function, to differentiate between normal subjects and patients with HH	Reduced or no LH, FSH, and oestradiol response; occasionally used to evaluate dynamic HPG axis function, to differentiate between normal subjects and patients with HH
Expected oestrogen/ progestogen challenge test results (in case of secondary amenorrhea and a negative pregnancy test, if no withdrawal bleeding)	Not indicated	Not indicated	Not indicated	Usually withdrawal bleeding	Usually withdrawal bleeding	Usually withdrawal bleeding

HPG, hypothalamic-pituitary-gonadal; T, testosterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SHBG, sex hormone-binding globulin; PRL, prolactin; AMH, anti-Müllerian hormone; GnRH, gonadotropin-releasing hormone; HH, hypogonadotropic hypogonadism. [1] Normal level for age-adjusted reference range.

Table 2. Endocrine complications of the common treatments for parasellar lesions

Treatment	Associated endocrine complications
Cranial irradiation	Low dose (18–24 Gy): – Precocious puberty in girls – Growth hormone deficiency High dose (≥24 Gy): – Precocious puberty in both sexes – Central hypothyroidism – Central hypoadrenalism – Delayed puberty – hypogonadism (≥30 Gy) – Hyperprolactinaemia (≥50 Gy) – Hypothalamic obesity (≥50 Gy)
Surgery in the hypothalamic-pituitary region	Hypopituitarism Hyperprolactinaemia Precocious puberty Absent/delayed puberty due to hypogonadism Hypothalamic obesity Diabetes insipidus
Alkylating agents	Primary hypogonadism Delayed puberty (especially in girls)
Anti-CTLA-4-antibody therapy	Hypopituitarism due to hypophysitis Thyroid dysfunction Primary adrenal insufficiency Hyperglycaemia
Glucocorticoids	Hypogonadism Delayed puberty Growth failure

stereotactic techniques (stereotactic radiosurgery or fractionated stereotactic radiotherapy). The aim is to deliver high radiation doses with a steeper dose gradient between the tumour and the surrounding neurovascular structures, thus reducing the long-term adverse effects [35, 36].

The secretion of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) follows a pulsatile rhythm, which is responsible for the efficient development of the reproductive system [37]. Radiation-induced gonadotropin deficiency shows a wide range of clinical expression, from subclinical impairment to severe forms. Generally, the cumulative incidence of gonadotropin deficiency during long-term follow-up is about 20–50%, regardless of whether radiotherapy was received in childhood or adulthood [38]. Disturbances of the pulsatile rhythm of FSH/LH production can affect puberty, fertility and libido in both males and females [39].

Chemotherapy, Immunological Treatment and Their Effects on the Hypothalamic-Pituitary-Gonadal Axis

In men, even low doses of alkylating agents such as temozolomide can exert cytotoxic effects on Sertoli, Leydig and germ cells. In women, they are responsible for a higher age-adjusted odds ratio of ovarian failure [40, 41].

The increasing use of immunological treatments has resulted in a growing number of reports of endocrine side effects, including hypophysitis [42]. Specific pituitary side effects have been described with CTLA4-blocking antibodies such as ipilimumab and tremelimumab. These can cause autoimmune diseases in up to 70% of patients [43, 44], of whom about 17% may present autoimmune hypophysitis during treatment. Patients developing hypophysitis may also develop LH and FSH deficiencies as well as adrenocorticotropin hormone, thyroid-stimulating hormone (TSH) and in some cases growth hormone (GH) deficiency (GHD), diabetes insipidus (DI) or syndrome of inappropriate antidiuretic hormone secretion [45–47]. The onset of hypophysitis and hence of hypopituitarism should be promptly diagnosed and treated [48]. HH has been described in 83–87% of male patients with hypophysitis treated with anti-CTLA4 antibodies [49]. Moreover, we should consider the effects of long-term treatment with glucocorticoids, used in cancer patients for multiple reasons such as for the anti-inflammatory action in the management of peritumoural brain oedema, to prevent nausea, vomiting, and hypersensitivity reactions to treatment with chemotherapy or radiation. This treatment can lead to suppressed gonadotropin secretion, and therefore to hypogonadism and delayed puberty [41, 50].

Long-Term Effects of Parasellar Lesion Treatments on Male Gonad Function

Male Central Hypogonadism

Boys presenting hypogonadism secondary to neurosurgery or radiotherapy at the time of normal puberty must undergo treatment to induce puberty. This is particularly important to achieve normal testicular volumes, penile length and secondary sexual characteristics [51]. Sex steroid replacement in males may be started from around 13 years, depending on the family history of pubertal development, psychosocial development, height and skeletal maturation [26]. The therapy usually involves testosterone esters given by intramuscular injection, but recent studies also call for the use of other tes-

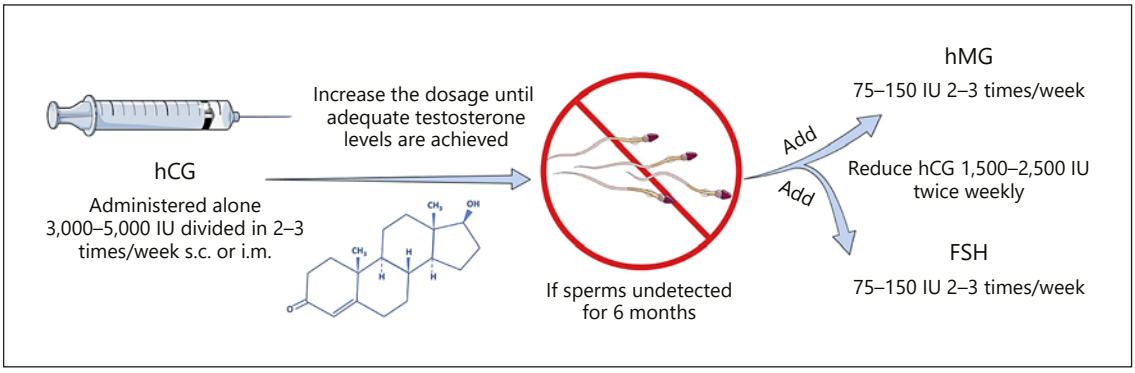

Fig. 1. Treatment of infertility in men with hypogonadotropic hypogonadism. This figure was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com. hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; FSH, follicle-stimulating hormone.

tosterone formulations such as transdermal gels that can be started when about 50% of the adult dose with i.m. testosterone has been achieved [52, 53].

Depending on the formulation used (testosterone enanthate, cypionate and propionate), the starting dose is normally 50–100 mg by i.m. injection every 4 weeks for 3–6 months, which is usually enough to achieve early virilization and growth without undesirable effects on epiphyseal maturation and bone age [52, 54]. After these first 6 months, the testicular volume should be rechecked, and if it is still <8 mL, a new treatment cycle and a gradually increased dose over 2–3 years is recommended to achieve normal growth and pubertal development, until the normal dose for adults is reached [52].

Puberty in adolescent males can also be induced with human chorionic gonadotropin (hCG), either as monotherapy or in combination with recombinant FSH. This might result in better testicular growth and penile length [55, 56], and is also the preferred approach to safeguard reproductive capacity, because early induction of spermatogenesis may increase sperm production and reduce the time required for the future appearance of sperm [55]. There is now an increasing consensus that puberty in HH should be initiated with gonadotropins, with testosterone priming only if delayed puberty is suspected. This approach is based on better outcomes in terms of testicular volume and spermatogenesis. Some recent evidence suggests that FSH should be given prior to hCG or testosterone to increase the sperm population, thus improving the response to subsequent stimulation [52, 57]. It is essential to consider the need for a prostate check-up before starting testosterone therapy [58–60].

Male Infertility

In adult men with secondary hypogonadism, testosterone treatment should be started soon after glucocorticoid and levothyroxine replacement therapy if multiple pituitary deficiencies are present [61, 62], but stopped before trying to conceive [63]. At this point, sperm production can be stimulated to restore fertility. Gonadotropin treatment results in the appearance of sperm in the ejaculate in up to 90% of subjects [64]. The first-line treatment is always hCG, for many reasons: it has the same biological activity as human LH, but with a longer half-life; it stimulates the Leydig cells to secrete testosterone; and it also increases the intratesticular testosterone concentration, which is essential for spermatogenesis [65, 66]. hCG is usually started intramuscularly at an initial dose of 3,000–5,000 units, divided into 2–3 doses a week. Blood testosterone concentrations should be checked every 1–2 months, and if not in the normal range, the hCG dose should be increased accordingly. The total sperm number is measured every 1–3 months once a normal serum testosterone concentration has been achieved, but it is not used as a parameter for tailoring hCG doses [67]. If the total sperm number has not reached half-normal values and/or pregnancy has not been achieved within 6 months of hCG treatment, recombinant human FSH or human menopausal gonadotropin (which contains both FSH and LH) can be added. The initial dose is 75–150 units 3 times a week, and again, the total sperm number should be measured every 1–3 months.

The treatment of infertility in men with HH is summarized in Figure 1. The time to achieve a near-normal

total sperm number in the ejaculate differs from patient to patient, but it can take up to 18–24 months [68].

Gonadotropin therapy is effective in inducing spermatogenesis in HH from both hypothalamic and pituitary causes. A better response has been obtained in patients with postpubertal onset of HH, in subjects with lower gonadotropin levels at enrolment and in patients with a pure secondary hypogonadism origin (low gonadotropins) [69]. The addition of FSH to hCG was associated with a better outcome, with similar results achieved for different FSH preparations (urinary derived, highly purified or recombinant) [69]. Other baseline predictors of successful spermatogenesis induction are a testicular volume >4 mL, a serum inhibin B level >60 pg/mL and the absence of previous cryptorchidism [70]. It should also be borne in mind that the outcome of gonadotropin therapy does not seem to be affected by previous testosterone replacement therapy.

The current 69–81% success rate for achieving spermatogenesis confirms the efficacy of gonadotropin replacement therapy in HH patients [69, 71]. Various studies report a mean sperm concentration of about 6 million per millilitre after gonadotropin treatment, which is usually considered sufficient to achieve fertility in HH patients [72, 73].

Although spontaneous conception might not be possible, pregnancy can often be achieved with the help of assisted reproductive technology (ART) or intrauterine insemination [74]. It has been reported that gonadotropin treatment improves the results of testicular sperm extraction/intracytoplasmic sperm injection, which can be performed in HH patients showing persistent azoospermia after hormone therapy [75, 76].

Cryopreservation of sperm should generally be offered before any chemotherapy, and above all once a normal sperm count has been achieved. Virilization can be maintained in men not wishing to have more children by continuing hCG alone or better returning to testosterone therapy.

Long-Term Effects of Parasellar Lesion Treatments on Female Gonad Function

Early Puberty

Treatment of intracranial tumours in prepubescent children can lead to abnormalities of puberty. Cranial irradiation can cause early puberty, mainly due to hypothalamic dysfunction [39]. Low doses (18–24 Gy) are associated with precocious puberty only in girls, while higher doses affect both sexes [77]. In girls with precocious puberty, depot GnRH analogues are the standard of care [41].

Female Central Hypogonadism

The risk of hypogonadism is related to age, pubertal development at the time of diagnosis, tumour site, treatment type and dosage [41]. The timing and dosage in patients with HH are the same as for girls with Turner syndrome or other causes of premature ovarian insufficiency [26].

In girls with a diagnosis of HH secondary to parasellar lesion treatment, oestrogen replacement therapy should be started at the age of 12–13 years [78], beginning at a low dose (one-eighth to one-quarter of the adult dose) and increasing it gradually to full adult replacement levels. A possible dose regimen is a patch containing 25 μg of 17β-oestradiol/24 h cut into 4 equal-sized pieces, applying one to the skin before going to bed and removing it the following morning. After 4–6 months the dose can be increased to 2 pieces at night, with one piece being removed the following morning and the other remaining on the skin all day. This dosage is usually increased about every 4–6 months, to one patch of 25–100 μg positioned continuously and changed twice a week. Alternatively, 0.5 mg of oral 17β-oestradiol can be taken every day or every other day as an initial dosage, increasing gradually [79].

When "breakthrough" bleeding occurs or after 1 or 2 years, oestrogen treatment with cyclic progesterone should be initiated to avoid endometrial hypertrophy [52, 79]. Progesterone can be cycled using either medroxyprogesterone at 5–10 mg or micronized progesterone at 100–200 mg for 10–14 days [52, 79]. In cases of simultaneous GHD, it might be decided to start GH replacement therapy before oestrogen replacement to ensure an adequate pubertal growth rate; however, this choice should be made on a case-by-case basis [26].

If hypogonadism arises after puberty, HRT is necessary. HRT until or beyond the age of natural menopause may reduce the risk of cardiovascular disease and mortality [61] and alleviates the vasomotor symptoms of hypooestrogenism. Oestrogen replacement may involve sequential oestrogens plus progesterone for 10–14 days or combined hormonal contraceptive pills. Oestrogen replacement therapy in hypogonadal women also protects against bone fractures [80].

Many different oestrogen formulations are available, including oral and transdermal, topical gels and lotions, intravaginal creams and tablets, and vaginal rings. When compared with transdermal formulations, oral oestro-

gens have unfavourable effects on lipid metabolism, inflammation and coagulation factors [81, 82]. Oral oestrogens significantly increase thyroid-binding globulin and cortisol-binding globulin (CBG) production and may also reduce IGF-1 levels. An increase in levothyroxine, glucocorticoids and GH doses may therefore be required in patients with hypothyroidism, adrenal insufficiency and GHD, respectively [22, 61]. Furthermore, the increase in CBG in response to oral oestrogens may give falsely normal levels of serum cortisol in patients with secondary adrenal insufficiency. Ethinyl oestradiol exerts a stronger effect than natural oestradiol on hepatic metabolism [83]. Progestogen should be given in combination with oestrogen therapy to prevent endometrial hyperplasia in women with an intact uterus [84]. The combined oestrogen-progestin contraceptive pill is sometimes better accepted by younger women [25]. There is a lack of specific studies on patients with central hypogonadism comparing the effects of sequential replacement of oestrogens and progestins and combined oestrogen-progestin contraceptive pills. The published evidence in relation to HRT in patients with HH refers to women with primary hypogonadism.

It should be noted that poor libido in women with combined gonadotropins and adrenocorticotropin hormone deficiencies may be due to androgen deficiency [25]. At present, the evidence-based indication for testosterone therapy in women is hypoactive sexual desire disorder, diagnosed in postmenopausal women after a complete biopsychosocial assessment [85]. The Endocrine Society's guidelines recommend against the routine use of dehydroepiandrosterone and testosterone in women with hypopituitarism or adrenal insufficiency, due to limited data concerning its effectiveness and safety [61]. There is a lack of dedicated studies on androgen therapy in women with central hypogonadism associated with hypoadrenalism.

Female Infertility

Women and girls with parasellar lesions are at risk of infertility because of the potential detrimental effects of surgery and radiotherapy on the hypothalamic-pituitary axis. Retrospective studies report pregnancy rates of between 47 and 76% amongst women with hypopituitarism [86–90]. In childhood, both hypopituitarism and isolated HH may lead to smaller uterine dimensions and ovarian volume compared with healthy controls [91]. When compared with women with isolated HH, patients with combined pituitary hormone deficiencies involving HH have fewer ovulatory cycles and worse pregnancy rates after controlled ovarian stimulation [87, 88]. To achieve pregnancy, patients with HH need ovulation induction or ART [92, 93]. Given the improved prognosis of some parasellar lesions and improvements in ART, fertility preservation strategies such as embryo and oocyte cryopreservation should be performed before radiotherapy or chemotherapy [39]. Embryo cryopreservation is the most effective option, while oocyte cryopreservation is used for prepubertal girls and women without a partner or sperm donor or with ethical objections to embryo storage. Both techniques include controlled ovarian hyperstimulation and oocyte retrieval. Ovarian tissue cryopreservation has only been performed under experimental protocols [41].

Women with reduced pituitary gonadotropic function due to pituitary diseases cannot benefit from pulsatile GnRH treatment to induce ovulation, although, conversely, this can be successful in women with hypothalamic amenorrhoea [94]. Different controlled ovarian stimulation (COS) protocols have been proposed for women with HH, involving human menopausal gonadotropin alone or combined with urinary FSH, recombinant FSH or low-dose hCG. Other protocols involve recombinant FSH with LH. COS protocols for assisted reproduction in women with HH are described in Table 3. The reported pregnancy rates after COS amongst HH women vary wildly, from 19.4 to 100%, with a 3.6–41.7% risk of multiple pregnancies [88–90, 95–100]. Higher gonadotropin doses are generally used than in patients with other causes of infertility [101]. Antral follicle count, ovarian volume and anti-Müllerian hormone levels are not useful to predict treatment response in women with HH [102].

Other Endocrine Effects Affecting Fertility

Hyperprolactinaemia can develop after surgery, after any disease disrupting pituitary stalk integrity and after hypothalamic irradiation with ≥50 Gy. It is associated with delayed puberty, menstrual irregularity, galactorrhoea, decreased libido, sexual dysfunction and infertility. Dopamine agonists can restore gonadal function [41].

It is well known that GH affects both male and female fertility [103]. GH acts on the testes both directly and indirectly via IGF-1, promoting sperm production, mostly through autocrine and paracrine functions [104]. In male patients with GHD, GH therapy seems not to affect testosterone levels [105]. In patients with HH, adjuvant GH therapy would seem to improve sperm motility in non-responders to gonadotropins, even though the data are not univocal [106, 107]. Isolated GHD in girls during

Table 3. Main controlled ovarian stimulation protocols for assisted reproduction in women with hypogonadotropic hypogonadism

	Characteristics	Studies [Ref.], year type	Patients, *n*	Doses	Ovulation rate, %	Pregnancy rate, %	Multiple gestations, %
hMG	Fixed LH/FSH ratio (1:1) Easy availability and low cost Daily subcutaneous administration started between menstrual cycle days 3 and 7 Dose incrementation of approximately 33% based on ultrasound findings Higher doses are needed for HH than for PCOS	White et al. [89], 2018 Retrospective study	80 HH (7 with pituitary deficiency following neurosurgery)	Starting dose of hMG: median 113 IU/day 2,500 IU of hCG administered at follicular maturation time to trigger ovulation	84	65	5
		Martin et al. [95], 1993 Retrospective study	30 HH (11 had a history of pituitary tumours)	Starting dose of hMG: 150 IU/day 3,000–5,000 IU of hCG at follicular maturation time to trigger ovulation	97	72	14.8
		Correa et al. [88], 2017 Prospective study	5 childhood-onset combined pituitary hormone deficiency	Starting dose of hMG: 75 IU/day (IUI) to 150 IU/day (IVF) 250 μg of recombinant hCG administered at follicular maturation time to trigger ovulation	/	100	20
		Balen et al. [130], 1994 Retrospective study	77 HH	Starting dose of hMG: 75 IU	75.2	83	3.6
hMG + uFSH	Step-up protocol uFSH has lower cost than rFSH	Pandurangi et al. [96], 2015 Retrospective study	7 HH	hMG 75–150 IU + uFSH 150–225 IU Ovulation was induced by a single IM administration of uhCG 10,000 IU	70	68.6	14.2
hMG + rFSH	Longer stimulation and duration and higher gonadotropin dose in HH patients than in patients with unexplained infertility or tubal factor infertility	Kumbak and Kahraman [97], 2006 Retrospective study	27 HH	hMG 300–600 IU/day + rFSH 150–450 IU An injection of 10,000 IU of hCG was administered to trigger ovulation	72	59	3.7
		Ghaffari et al. [98], 2013 Retrospective study	81 HH	Daily hMG (75 IU ± rFSH 75 IU) Ovulation was triggered with 10,000 IU of hCG	93.8	19.4	5.5
hMG + low-dose hCG	hCG has a lower cost, longer half-life and higher affinity for receptors than rLH HH patients require a longer duration and higher dose of HMG, even with the addition of low-dose hCG, than patients with tubal factor infertility	Jiang and Kuang [99], 2018 Retrospective study	46 HH	hMG 150 IU/day or 225 IU/day + hCG injections 50–300 IU/day Ovulation was triggered by hCG 5,000 IU	64.2	59.5	41.7
rFSH + rLH	Safe and effective in inducing follicular development in HH women with marked gonadotropin deficiency FSH and LH dose ratio can be altered to 2:1 Higher cost than hMG	Kaufmann et al. [131], 2007 Open-label, RCT	31 HH	A fixed dose of lutropin alfa 75 IU and an individualized dose of follitropin alfa (initial dose 75–150 IU and up to 225 IU once daily SC) 10,000 IU of hCG administered at follicular maturation time to trigger ovulation	92	59.3	19.3
		Carone et al. [132], 2012 Randomized, open-label study	17 HH	150 IU r-hFSH and 75 IU r-hLH daily Ovulation was induced by a single administration of 10,000 IU of hCG	70	55.6	11.7
Pulsatile GnRH	Suitable only for women with an intact pituitary gland Maintains normal pituitary-ovarian feedback Need to attach a pump, which can cause discomfort More expensive than hMG injections Reduces the risk of multiple pregnancies and ovarian hyperstimulation	Martin et al. [95], 1993 Retrospective study	41 HH	75–250 ng/kg	93	96	8.3

FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; HH, hypogonadotropic hypogonadism; hMG, human menopausal gonadotropin; IM, intramuscular; IUI, intrauterine insemination; IVF, in vitro fertilization; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; rFSH, recombinant FSH; r-hFSH, human recombinant FSH; r-hLH, human recombinant LH; rLH, recombinant LH; SC, subcutaneous; uFSH, urinary FSH.

childhood is associated with a small uterus, suggesting that GH might have an independent effect in determining uterus size [91]. GH is involved in ovulation, oocyte quality and competence, increases in follicular growth, and modulation of progesterone and oestradiol release through both GH and IGF-1 receptor expression on ovarian cells [103, 108, 109]. Spontaneous conception can be achieved by women with GHD as long as the hypothalamic-pituitary-gonadal (HPG) axis is intact and adequate HRT is given [110]. Although there are numerous articles discussing GH supplementation during ART for women with normal pituitary function [111], the only evidence of improved oocyte quality after GH administration in women with GHD comes from case reports [109].

TSH deficiency usually occurs after gonadotropin and GHD in patients with hypopituitarism. There is little information on how central hypothyroidism affects fertility, although thyroid hormones have an important role in

Table 4. Suggested management of hypopituitarism in pregnancy

Disease	Preconception	1st trimester	2nd trimester	3rd trimester	Delivery	Post-partum
HPA axis	Hydrocortisone 10–12 mg/m^2/day (commonly 15–20 mg/day) in 2 or 3 divided oral doses Cortisone acetate (once daily 25–37.5 mg/day), prednisone or prednisolone (3–5 mg/day) could potentially be used[1] Avoid dexamethasone, as it is not inactivated by 11β-HSD2	Continue preconception doses No need to increase GC replacement dose unless there is evidence of intercurrent illness Consider parenteral GCs for intractable vomiting	No need to increase GC replacement dose unless there is evidence of intercurrent illness	Adjust according to clinical course Usually no need to increase GC replacement dose, but some authors suggest a 20–40% increase	100 mg hydrocortisone IM (or IV) on onset of active labour followed by hydrocortisone 200 mg every 24 h via continuous IV infusion or 50 mg every 6 h is recommended	Adjust according to clinical condition or intercurrent conditions For the first 2–4 days, maintain a double oral dose If there are no complications, the preconception dose can be restored thereafter
	Patients should be advised of possible adrenal crises and treated accordingly with stress dose covering GC dose adjustment in case of stressful situations (double up the dose for the duration; give parenteral GC in case of vomiting or emergency situations)					
Thyroid axis	Insufficient data regarding effects of central hypothyroidism on fertility Thyroid hormones seem to have an important role, so thyroid function must be taken into account when conceiving is difficult	Patients treated for primary thyroid failure need a 20–50% increase in hormone replacement doses once pregnancy is established Secondary hypothyroidism might not require an increased dose Keep free T_4 and total T_4 in upper half of normal range Monitor every 4–6 weeks	Keep dose stable	Keep dose stable	Keep dose stable	Return to preconception dose
GH axis	GH treatment might improve fertility	If GH replacement is not contraindicated, some studies suggest continuing the preconception GH dose GH not approved for pregnancy by FDA and EMA	Do not start GH treatment If previous GH treatment is continued, GH dose should be reduced by 30–50%	No need for GH Previous GH treatment should be stopped	No need for GH	Return to preconception dose
Gonadal axis	This axis is physiologically suppressed from the very beginning of pregnancy; no need for replacement therapy					
Desmopressin	No need to increase dose	Dose increase as needed in relation to clinical setting Pregnancy may unmask mild forms of diabetes insipidus	–	–	Dose adjusted in line with fluid requirement and sodium levels	Return to preconception dose

GC, glucocorticoid; GH, growth hormone; HPA, hypothalamic-pituitary-adrenal; HSD, hydroxysteroid dehydrogenase; IM, intramuscularly; IV, intravenous(ly); T_4, thyroxine. [1] Prednisone and cortisone both require activation by maternal 11β-HSD1 (to form active prednisolone and cortisol respectively); women on other GCs should be switched to hydrocortisone.

both female and male fertility [112–114]. Thyroid function must therefore be taken into account when attempting to restore fertility. Finally, hypothalamic obesity, which affects 30–77% of patients after craniopharyngioma treatment, could potentially interfere with normal fertility [115].

Managing Pregnancy

The efficacy of the aforementioned treatment protocols and the rapid development and successful application of ART have led to an increase in the number of women achieving fertility and pregnancy despite underlying hypopituitarism [116]. Research over the last decade has filled the gaps in our understanding of the mechanism governing hormonal changes during pregnancy, the role of the placenta as a true endocrine gland and the interaction between the maternal and fetal endocrine systems [117]. Hormone replacement in endocrinology aims specifically to restore, as far as possible, the physiological hormone secretion pattern [61] and patient well-being. Generally speaking, there are no randomized controlled trials on pituitary hormone replacement during pregnancy, and decisions are based mainly on expert opinions and observational studies, which usually try to mimic the physiology of normal pregnancy. Table 4 presents suggestions for the management of hypopituitarism in pregnancy.

Glucocorticoid replacement during pregnancy is essential when hypothalamic-pituitary-adrenal function is impaired [118]. Steroid replacement in this context should take into account the potentially greater requirement secondary to the pregnancy-induced changes to the hypothalamic-pituitary-adrenal axis (increased CBG, increased placental corticotropin-releasing hormone secretion [119] and 2- to 3-fold increases in total cortisol concentrations, peaking in the 2nd and 3rd trimesters) [120], aiming to avoid undesirable effects on the fetus. Women appropriately treated with replacement therapy can expect to have uneventful pregnancies of a normal duration, with no fetal compromise. However, unrecognized or inappropriately treated adrenal insufficiency in pregnant women can lead to harmful effects on both the mother

(increased morbidity and mortality) and the fetus (reduced birth weight, neurodevelopmental problems and cardiometabolic diseases) [90].

In principle, various glucocorticoid formulations (hydrocortisone, cortisone acetate, prednisone and prednisolone) can be used during pregnancy. However, prednisone and cortisone acetate both need to be activated by maternal 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1. For this reason, and because of its deactivation by placental 11β-HSD type 2, the only recommended formulation is hydrocortisone, as it cannot cross the placenta into the fetal circulation and does not cause any undesirable effects in the fetus.

Current knowledge about steroid replacement during pregnancy is mainly derived from data obtained from Addison's disease, but when considering a replacement for a secondary form of adrenal insufficiency, it should be borne in mind that lower doses are normally needed, without any mineralocorticoid replacement. Hydrocortisone is usually prescribed 3 times daily to follow the circadian rhythm, with a suggested dose of 12–15 mg/m^2/day, tapered according to clinical judgment, by closely monitoring signs and symptoms of over- and underreplacement [121]. Although there is no universal consensus, some experts suggest increasing the total dose by 20–40% in the last trimester [122], in line with the physiological increase in free cortisol during this trimester. Emergency steroid cover during the active phase of labour, delivery and caesarean section is crucial, as these are all stressful situations requiring intravenous administration of hydrocortisone (50 mg in the second stage of labour/delivery, and 50–100 mg preoperatively and every 8 h postoperatively for caesarean section). After delivery, double the pre-conception dose should be given for the first 2–4 days, and, provided that no complications are affecting the mother, a pre-pregnancy dose can be safely restored thereafter [123]. It should be noted that dexamethasone is not deactivated by placental 11β-HSD type 2, and so is contraindicated during pregnancy.

Thyroid hormones are essential for normal fetal cognitive development. The increased demand for thyroid hormones during pregnancy is normally guaranteed by binding of the placental hCG to the TSH receptor, leading to a physiological "hyperthyroidism," especially during the 1st trimester [124]. The current guidelines thus suggest that patients treated for primary thyroid failure need a 20–50% increase in their HRT doses once pregnancy is established [125]. However, this may not fully apply to secondary hypothyroidism. If thyroid function is intact, hCG stimulation could guarantee normal thyroid hormone production, meaning that replacement therapy might not be needed. In these cases, free and total thyroxine should be carefully monitored, aiming to maintain their levels in the upper half of the normal range [126]. After delivery, thyroid replacement doses should be reduced to pre-pregnancy doses.

In contrast, GH replacement therapy during gestation is controversial. Current evidence on the physiology of GH secretion during pregnancy shows that GH is still secreted until mid-gestation; therefore, continuation of GH therapy, at least in the 1st trimester, could be theoretically advocated. For this reason, some experts continue GH therapy at the same dose in the 1st trimester and at half the dose in the 2nd trimester, stopping it altogether in the last trimester [127]. However, no randomized controlled trials have been conducted on the effects of GH therapy during pregnancy, and current Endocrine Society guidelines recommend stopping GH during conception and pregnancy [92].

Physiologically, the HPG axis is suppressed from the very beginning of pregnancy, so no treatment is recommended in relation to hormones.

Desmopressin therapy can be safely continued or started during pregnancy [61]. Due to the naturally increased total body water, expanded plasma volume and increased maternal vasopressin in pregnancy, dose adjustment may be necessary for some but not all patients with previous DI. Clinicians should monitor the signs and symptoms of DI both clinically (polyuria-polydipsia) and biochemically (plasma osmolality and serum sodium) [128], as the water deprivation test is not recommended [129].

Conclusions

In recent decades, progress in parasellar tumour diagnosis and treatment has led to a great improvement in survival rates. Strategies for identifying patients with delayed puberty and instituting timely pubertal induction in adolescence can significantly improve long-term sexual and reproductive function. A correct identification of delayed puberty and personalization of puberty induction therapy with androgens and/or gonadotropins are crucial with these patients. Long-term physiological testosterone replacement is necessary for men with permanent HH, to substitute HPG function and to reduce comorbidities associated with HH.

In girls with a diagnosis of HH secondary to parasellar lesion treatment, oestrogen replacement therapy should

be promptly started with the proposed protocols; if hypogonadism arises after puberty, HRT is necessary until or beyond the age of natural menopause to protect female patients from metabolic, cardiovascular and bone diseases associated with HH.

Post-treatment preservation of fertility and quality of life is therefore crucial. Whenever possible, fertility aspects should be discussed before starting therapies leading to hypogonadism and infertility. Unfortunately, about 40% of cancer survivors report that no fertility counselling was offered after their diagnosis. Fertility preservation strategies are available, and several studies are evaluating further new alternatives. A multidisciplinary approach involving oncologists, radiotherapists, endocrinologists, gynaecologists and fertility specialists is essential to improve the awareness and availability of these options. As ART regimens continuously change and fertility options improve, future studies on patients with hypopituitarism are needed to find a patient-tailored strategy for restoring hormonal function, when possible, and preserving the patient's reproductive potential.

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Author Contributions

E.S.: substantial contributions to conception of the manuscript, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted. M.M. and R.P.: substantial contributions to conception of the manuscript, acquisition of data, analysis and interpretation of data, and drafting the article. A.C. and E.G.: substantial contributions to acquisition of data, analysis of data, and revising the manuscript critically for important intellectual content. D.G.: substantial contributions to conception of the manuscript, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted. A.M.I.: substantial contributions to conception and design of the manuscript, drafting the article and revising it critically for important intellectual content, and final approval of the version to be submitted.

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