| | Disorders | Etiology | | Work-up | Management |
|---|---|---|---|---|---|
| WHO Classification Group I: Hypogonadotropic Hypogonadal Anovulation | **Idiopathic hypogonadotropic hypogonadism (IHH)** | ***Normosomic*** Mutations of GNRHR, ANOS1, FGF8/FGFR1, TACR3, CCDC141, NELF[4] | ***Kallmann*** Interrupted GnRH neuron migration from nasal placode; FGFR1, ANOS1 (KAL1), FGF8, FGF17, IL17RD, DUSP6, SPRY4, FLRT3, KLB, PROK2, PROKR2, HS6ST1, CHD7, WDR11, SEMA3A, SEMA3E, IGSF10, SMCHD1, CCDC141, FEZF1, HESX1 | - Brain MRI<br>- FSH, LH | - Transdermal estradiol patch; gradually increase dose<br>- Conjugated equine estrogen with Cyclic medroxyprogesterone 10mg 12-14 days/month<br>- combined oral contraceptive pill<br>- Fertility treatment: recombinant FSH, human menopausal gonadotropin |
| | **Septo-Opto Dysplasia** | - Vascular insult in 6th-7th week of embryogenesis<br>- HESX1 mutation<br>- Associated risk factors:<br>- 1st trimester bleeding<br>- Illicit drug use<br>- Primiparity | | - Brain MRI<br>- FSH, LH | - Neurodevelopmental monitoring<br>- Combined oral contraceptive pill<br>- Estradiol patch or oral conjugated equine estradiol with cyclic medroxyprogesterone |
| | **Panhypopituitarism** | - Pituitary tumors<br>- Traumatic brain injury<br>- Inflammatory changes ((Mycobacterium Tuberculosis, histoplasmosis, syphilis, viruses, protozoa, lymphocytic hypophysitis)<br>- Infiltrative disease (Histiocytosis, hemochromatosis, sarcoidosis)<br>- Pituitary apoplexy, Sheehan's syndrome<br>- Congenital (genetic mutation of HESX1, PROP1, and Pit-1)<br>- Empty Sella Syndrome | | - Brain MRI<br>- FSH, LH<br>- TSH, ACTH | - Combined oral contraceptive pill<br>- Estradiol patch or oral conjugated equine estradiol with cyclic medroxyprogesterone<br>- Correct other endocrinopathies<br>- Fertility treatment: recombinant FSH, human or menopausal gonadotropin |
| | **Craniopharyngioma** | - Embryonic theory: arises from remnants of Rathke's pouch<br>- Metaplastic theory: metaplasia of squamous epithelial cell rests from stomodeum<br>- Mutations in CTNNB1 that encodes β-catenin | | - Brain MRI<br>- FSH, LH | - Radiotherapy or subtotal resection<br>- Fertility treatment: recombinant FSH, human menopausal gonadotropin |
| | **Langerhans Histiocytosis X** | - Somatic mutations gain of function in BRAF gene in 50% of cases | | - Brain MRI<br>- FSH, LH<br>- Prolactin, TSH, ACTH<br>- Basic metabolic profile | - Radiotherapy<br>- Correct endocrinopathy<br>- Fertility treatment: human menopausal gonadotropin (hMG) |
| WHO Classification Group II: Irregularities in HPO Axis | **Polycystic Ovarian Syndrome** | - Multifactorial<br>- Candidate genes mutated: GLUT4, miR-93 | | - Total testosterone<br>- 17-hydroxyprogesterone<br>- Dehydroepiandrostene-dione sulfate<br>- 2-hour glucose tolerance test<br>- Lipid panel<br>- Transvaginal ultrasonography | - Combined oral contraceptive pill<br>- Fertility treatment: First line- letrozole Second line- clomiphene citrate |
| | **Hyperprolactinemia** | - Prolactinoma<br>- Primary hypothyroidism<br>- Autoimmune disorders<br>- Chronic renal failure<br>- Psychotropic medications | | - Prolactin<br>- TSH<br>- MRI of the pituitary fossa | - Cabergoline<br>- Bromocriptine<br>- Surgical decompression if medical management fails |
| | **Thyroid dysfunction** | ***Hyperthyroidism***<br>- Hashimoto's thyroiditis<br>- Lymphocytic thyroiditis<br>- Radiation therapy<br>- Surgery<br>- De Quervain<br>- Infiltrative sarcoidosis<br>- Hemochromatosis<br>- Drugs (Lithium, Amiodarone) | ***Hypothyroidism***<br>-Graves disease<br>- Iatrogenic (drug induced, TKI, INFα)<br>- Inadequate Iodine<br>- Struma ovarii<br>- Infection | - TSH<br>- Total and free T4<br>- Consider total and free T3 | - Levothyroxine if hypothyroid<br>- Methimazole or propylthiouracil if hyperthyroid |
| | **Endometriosis** | - Multifactorial<br>- miR-135a overexpression<br>- Copy number variants: 1p36, 7p22.1 and 22q12 | | - Diagnostic laparoscopy | - Surgical ablation of lesions<br>- Ovulation induction agents |
| WHO Classification Group III: Hypergonadotropic Hypogonadal Anovulation | **Primary Ovarian Insufficiency** | - Genetic (Turner's, Fragile X)<br>- Acquired (autoimmune, environmental)<br>- Iatrogenic (chemotherapy agents, drugs, brain radiation) | | - AMH<br>- Karyotype<br>- FMR1 pre-mutation | - Combined oral contraceptive pill<br>- Estradiol patch or oral conjugated equine estradiol with cyclic medroxyprogesterone<br>Fertility treatment:<br>- Oocyte or ovarian tissue* cryopreservation<br>- IVF with donor oocytes<br>- Stem cell therapy*<br>- AUGMENT*<br>*still considered experimental |

Table S1. Summary of group I-III ovulation disorders including etiology, evaluation and management.