

THE MATURING WOMAN WITH RETT SYNDROME

From Puberty to Menopause

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Points for Discussion

- **Puberty, Menarche, and Menopause**
- **Seizure and Antiepileptic Medication Issues in Women**
- **Medications and Procedures for Menstrual Management**
- **Health Maintenance**

Puberty

Puberty

- **Series of predictable events**
 - achievement of fertility
 - development of secondary sexual characteristics
 - changes in body composition and growth
 - changes in most body systems
 - neuroendocrine and cardiovascular systems
 - bone size and mineralization
- **Physical changes categorized by Tanner stages (I-V)**

Changes with puberty

- **Body changes**
 - Growth spurt
 - Breast development/ hips widen
 - Pubic, underarm and leg hair thickens and darkens
 - Oily skin and hair/acne
 - Underarm odor
 - Vaginal discharge appears
- **Comfort and mood changes**
 - cramping, mood swings, irritability and fatigue even prior to menarche
- **Timeline of puberty to menarche → ~ 4 years**

Puberty: factors affecting onset

- Race
- Nutrition and % body fat
- Activity level
- Genetics
- Antiepileptic medications
- Anatomic/physiologic abnormalities
- Psychobiologic theory of stress
- Chemical exposure

Puberty in Rett Syndrome

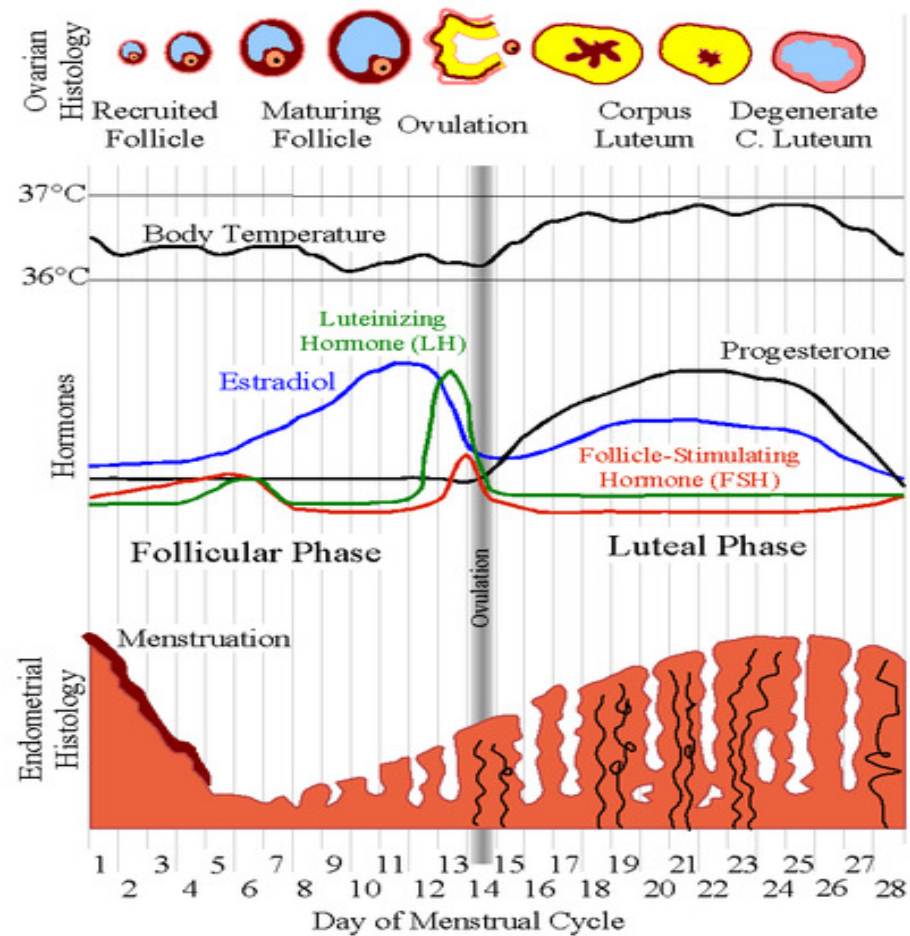
Natural History Study Data

- **US girls with RTT achieve Tanner II at an average age of 7.1 ± 2.5 years compared to general population average age 9.96 ± 1.8 years***
- **Pubertal growth spurt absent in RTT****

*Garcia-Rudaz et al. J Neuroendocrinology 21: 108-122 2009

** Tarquinio et al. Unpublished observations

Menstrual Cycle



(Average values. Durations and values may differ between different females or different cycles.)

Menarche

- **Marked by start of menstrual cycle**
- **May be fertile just prior to menarche**
- **Individual experience variable**

Menarche and Rett Syndrome (RTT) Natural History Study Data - 2011

**Based on 298 females with RTT who
have achieved menarche**

- **Mean age 12.43 (median 12.00) years +/- 2.3**
- **Median ages non-Rett**
 - **12.43 years US (2003) ***
 - **13.2 years NO (1993) ****

*Chumlea WC et al. *Pediatrics*, 2003 Jan:111(1):110:3

** Nafstad PB et al. *Tidsskr Nor Laegeforen*, 1993 155:604-606

Related Issues To Menstruation

- **Cramps**
 - Meds OTC or Prescription
 - Warm packs, baths and massage
- **PMS**
 - Tender breasts, bloating, irritability, low mood
 - Possible causes: Hormone fluctuations, changes in brain chemicals
- **Hygiene**
 - Menstrual flow is odorless until it comes in contact with air and bacteria
 - Bathing and meticulous personal care essential
- **Seizures**

Abnormalities in development (US statistics)

- **Considered delayed development**
 - no breast development by age 13
- **Precocious puberty**
 - AA → Breast *or* pubic hair <6 yrs
 - Caucasian → Breast *or* pubic hair <7 yrs
 - All → Breast *and* public hair <8 yrs
- **Primary amenorrhea**
 - no menses by age 15

**Puberty and
Menstruation are
NORMAL functions**

Hormones, Seizures, and Antiepileptic Medications

Relationship Between Seizures and Hormones

- **Hormones influence seizure occurrence**
 - *Estrogen* – excitatory affect on brain cells
 - *Progesterone* – inhibitory affect on brain cells
- **Seizures associated with ovulation or menstruation are called *catamenial epilepsy* and are caused by hormone fluctuations**

Catamenial Epilepsy

- **Seizures may increase during puberty**
 - **Hormone fluctuations, including low progesterone**
 - **Sleep disruption**
 - **Antiepileptic drug blood levels may be adversely affected by**
 - **Fluid retention**
 - **Rapid weight gain**
 - **Oral contraceptives**
- **Women with epilepsy are 4-7 times more likely to have irregular cycles**
- **Seizure and menstrual cycle diary**

Catamenial Epilepsy Treatment Options

- **Adjusting existing seizure medications during cycle**
- **Intermittent perimenstrual medications**
 - clonazepam (0.05-0.1mg/kg/day) or clobazam (5-10mg/day; up to 30mg/day)
- **Hormonal manipulation aimed at increasing progesterone**
 - Progesterone (days 10-26 of cycle)
 - Combination oral contraceptive (estrogen AND progestin)
- **Diuretics**
- **Sleep medications**

Medications and Procedures for Menstrual Management and Birth Control

Menstruation Management – *a very personal decision*

- **Non-interventional method**
- **Oral Contraceptives/Birth Control Pills**
- **Depo-Provera injection**
- **Topical skin patch**
- **Vaginal rings**
- **Intrauterine device (IUD)**
- **Endometrial ablation**
- **Hysterectomy**

Oral Contraceptives

- **Conventional – 21 or 28 day course, menstruation every month**
 - Yasmin[®], LoEstrin[®], Ortho Tricyclen[®], and Ortho Tricyclen Lo[®]
- **Newer – 84 day course, reduces menstruation 4X/year**
 - Seasonale[®], Seasonique[®]
- **Newest – taken daily and continuously, stops menstruation**
 - Lybrel[®]
 - Combination pills - estrogen and progestin
 - 'Minipill' - progesterone only

List of Combination Oral Contraceptives

- Alesse® (containing Ethinyl Estradiol, Levonorgestrel)
- Apri® (containing Desogestrel, Ethinyl Estradiol)
- Aranelle® (containing Ethinyl Estradiol, Norethindrone)
- Aviane® (containing Ethinyl Estradiol, Levonorgestrel)
- Azurette® (containing Desogestrel, Ethinyl Estradiol)
- Balziva® (containing Ethinyl Estradiol, Norethindrone)
- Beyaz® (containing Drospirenone, Ethinyl Estradiol, Levomefolate)
- Brevicon® (containing Ethinyl Estradiol, Norethindrone)
- Cesia® (containing Desogestrel, Ethinyl Estradiol)
- Cryselle® (containing Ethinyl Estradiol, Norgestrel)
- Cyclessa® (containing Desogestrel, Ethinyl Estradiol)
- Demulen® (containing Ethynodiol, Ethinyl Estradiol)
- Desogen® (containing Desogestrel, Ethinyl Estradiol)
- Enpresse® (containing Ethinyl Estradiol, Levonorgestrel)
- Estrostep® Fe (containing Ethinyl Estradiol, Norethindrone)
- Femcon® Fe (containing Ethinyl Estradiol, Norethindrone)
- Gianvi® (containing Drospirenone, Ethinyl Estradiol)
- Jolessa® (containing Ethinyl Estradiol, Levonorgestrel)
- Junel® (containing Ethinyl Estradiol, Norethindrone)
- Kariva® (containing Desogestrel, Ethinyl Estradiol)
- Kelnor® (containing Ethynodiol, Ethinyl Estradiol)
- Leena® (containing Ethinyl Estradiol, Norethindrone)
- Lessina® (containing Ethinyl Estradiol, Levonorgestrel)
- Leven® (containing Ethinyl Estradiol, Levonorgestrel)
- Levlite® (containing Ethinyl Estradiol, Levonorgestrel)
- Levora® (containing Ethinyl Estradiol, Levonorgestrel)
- Lo/Ovral® (containing Ethinyl Estradiol, Norgestrel)
- Loestrin® (containing Ethinyl Estradiol, Norethindrone)
- Loestrin® Fe (containing Ethinyl Estradiol, Norethindrone)
- LoSeasonique® (containing Ethinyl Estradiol, Levonorgestrel)
- Low-Ogestrel® (containing Ethinyl Estradiol, Norgestrel)
- Lutera® (containing Ethinyl Estradiol, Levonorgestrel)
- Lybrel® (containing Ethinyl Estradiol, Levonorgestrel)
- Microgestin® (containing Ethinyl Estradiol, Norethindrone)
- Microgestin® Fe (containing Ethinyl Estradiol, Norethindrone)
- Mircette® (containing Desogestrel, Ethinyl Estradiol)
- Modicon® (containing Ethinyl Estradiol, Norethindrone)
- MonoNessa® (containing Ethinyl Estradiol, Norgestimate)
- Necon® 0.5/35 (containing Ethinyl Estradiol, Norethindrone)
- Necon® 1/50 (containing Mestranol, Norethindrone)
- Nordette® (containing Ethinyl Estradiol, Levonorgestrel)
- Norinyl® 1+35 (containing Ethinyl Estradiol, Norethindrone)
- Norinyl® 1+50 (containing Mestranol, Norethindrone)
- Nortrel® (containing Ethinyl Estradiol, Norethindrone)
- Ocella® (containing Drospirenone, Ethinyl Estradiol)
- Ogestrel® (containing Ethinyl Estradiol, Norgestrel)
- Ortho Tri-Cyclen® (containing Ethinyl Estradiol, Norgestimate)
- Ortho Tri-Cyclen® Lo (containing Ethinyl Estradiol, Norgestimate)
- Ortho-Cept® (containing Desogestrel, Ethinyl Estradiol)
- Ortho-Cyclen® (containing Ethinyl Estradiol, Norgestimate)
- Ortho-Novum® 1/35 (containing Ethinyl Estradiol, Norethindrone)
- Ortho-Novum® 1/50 [DSC] (containing Mestranol, Norethindrone)
- Ovcon® (containing Ethinyl Estradiol, Norethindrone)
- Portia® (containing Ethinyl Estradiol, Levonorgestrel)
- Prevfem® [DSC] (containing Ethinyl Estradiol, Norgestimate)
- Quasense® (containing Ethinyl Estradiol, Levonorgestrel)
- Reclipsen® (containing Desogestrel, Ethinyl Estradiol)
- Safyral® (containing Drospirenone, Ethinyl Estradiol, Levomefolate)
- Seasonale® (containing Ethinyl Estradiol, Levonorgestrel)
- Seasonique® (containing Ethinyl Estradiol, Levonorgestrel)
- Solia® (containing Desogestrel, Ethinyl Estradiol)
- Sprintec® (containing Ethinyl Estradiol, Norgestimate)
- Sronyx® (containing Ethinyl Estradiol, Levonorgestrel)
- Tilia® Fe (containing Ethinyl Estradiol, Norethindrone)
- Tri-Ligest® Fe (containing Ethinyl Estradiol, Norethindrone)
- TriNessa® (containing Ethinyl Estradiol, Norgestimate)
- Tri-Norinyl® (containing Ethinyl Estradiol, Norethindrone)
- Triphasil® (containing Ethinyl Estradiol, Levonorgestrel)
- Tri-Prevfem® [DSC] (containing Ethinyl Estradiol, Norgestimate)
- Tri-Sprintec® (containing Ethinyl Estradiol, Norgestimate)
- Trivora® (containing Ethinyl Estradiol, Levonorgestrel)
- Velivet® (containing Desogestrel, Ethinyl Estradiol)
- Yasmin® (containing Drospirenone, Ethinyl Estradiol)
- Yaz® (containing Drospirenone, Ethinyl Estradiol)
- Zenchant® (containing Ethinyl Estradiol, Norethindrone)
- Zovia® (containing Ethynodiol, Ethinyl Estradiol)

Risks of Oral Contraceptives

- ***Common:*** dizziness, headache, nausea, mood changes, weight gain, breakthrough bleeding
- ***Rare:*** blood clots, high blood pressure, stroke, heart attack, gallstones

Cancer Risks of Oral Contraceptives

Yes or No?

- **Breast cancer**
 - No risk to ↑ risk
- **Ovarian cancer**
 - ↓ risk
- **Cervical cancer**
 - ↑ risk but r/t HPV (sexual activity)
- **Liver cancer**
 - ↑ risk in Caucasians but r/t duration and probably r/t co-existing hepatitis infections

Effects of Antiepileptic Medications on Oral Contraceptives

- **AED that increase breakdown of contraceptives, making them less effective**
 - carbamazepine (regular and extended release), oxcarbazepine, phenytoin, phenobarbital, primidone, topiramate
- **AEDs with no effect on contraceptives**
 - gabapentin, lamotrigine, levetiracetam, tiagabine, valproate and felbamate

Effects of Oral Contraceptives (OC) on Antiepileptic Medications

- ***Effect of OC on phenytoin***
 - Serum drug levels increased by estrogen
 - May require phenytoin blood level assessment after estrogen therapy begun
- ***Effect on valproate and carbamazepine***
 - No known effects from oral contraceptives

Effects of Oral Contraceptives (OC) on Antiepileptic Medications

- ***Effect on lamotrigine***
 - OC may increase breakdown of lamotrigine
 - Higher doses of lamotrigine may be required to have good seizure control
 - May experience large fluctuations of lamotrigine between OC active/placebo phase
 - Good argument for continuous OC (i.e. Seasonale[®], Seasonique[®], Lybrel[®])

Depo-Provera Injections

- Progesterone
- Must be given by RN or MD every 3 months
- Should prevent ovulation, but 30% continue to have regular cycle
- ****Affects bone density increasing risk of osteoporosis so NOT RECOMMENDED for use**
- Side effects
 - may be extreme and irreversible until medication wears off
 - include irritability, weight gain, irregular breakthrough bleeding

Vaginal Rings

- NuvaRing[®] vaginal ring
- Combination estrogen/progestin
- Not a daily pill
- “self-inserted” in vagina once a month X3 weeks – period every month
- Same risks as other combination OC - plus
 - Vaginal infections, irritations, and secretions

Topical Patches

- Ortho Evra[®] patch
- Combination estrogen and progestin
- Absorbed through skin, changed every week – period every month
- Exposed to 60% more estrogen
 - Results of studies ranged from an approximate doubling of risk of serious blood clots to no increase in risk in women using ORTHO EVRA[®] compared to women using birth control pills.

Endometrial Ablation

- **Outpatient surgery**
 - Laser, heat, electricity, freezing, or radiowaves
 - Local, spinal or general anesthesia
- **Mechanism of action**
 - Endometrium scars reducing flow
- **Permanently stops menstruation in about 50%, reduces flow in most of remaining 50%**
 - More effective in older than younger
 - Adjunctive use of gonadotropin-releasing hormone (Lupron) may improve effectiveness
- **Risks significant – permanent scarring of uterus, alteration in anatomy, laceration, burns, usual surgery risks**
- **Advantage – short recovery**

Hysterectomy

- **Surgical removal of uterus +/- ovaries**
 - Total – uterus and cervix
 - Subtotal – uterus only
- **Techniques**
 - Abdominal
 - Mini Laparotomy
 - Vaginal
 - Laparoscopy
- **Risks and Disadvantages**
 - Usual surgery risks
 - Long recovery, legal implications and costs

Menopause and Aging

**“Age is of no importance
unless you're a cheese.”**

Billie Burke

Menopause

- **Average age on onset - 51 years (40-65)**
- **Anecdotal reports with RTT suggest early aging in appearance, but unsure of impact on age of menopause**
- **Changes that occur**
 - **Ovaries stop making estrogen**
 - **Change in periods 1st sign - until they stop**

Menopause and Seizures

- **Generally occurs significantly earlier in women with high seizure frequency**
- **Reports of seizures during menopause vary**
 - 40% report worsening seizures
 - 27% report improvement of seizures
 - 33% report no change
- **Hormone replacement therapy associated with increase in seizures (more in those with catamenial epilepsy)**
- **In RTT, seizures diminish and EEG's tend to improve as women grow older**

Menopause Health Issues

- **Osteoporosis – long term AED increase risk**
- **Mood changes**
- **Hot flashes**
- **Increased chance of bladder infections**
- **Abnormal bleeding may occur**
- **Hormone replacement therapy may be given to offset symptoms such as hot flashes, bone loss, mood disturbances, but come with their own risks (increased seizures and cancers of breast and endometrium)**

Health Maintenance

US Health Care Fact

- **In the US, women with disabilities receive less breast and cervical health care as a result of environmental, attitudinal, and information barriers**
 - **Inaccessible health care facilities**
 - **Lack of disability awareness by clinicians**
 - **Dependence on others for self-exams**
 - **May be unable to report symptoms**

Wyoming Breast Health for Women with Disabilities Project

Resulting situation

Women with disabilities tend to be diagnosed with breast cancer at later stages and have higher mortality rates

Roetzheim, et al. J. of Health Care for the Poor and Underserved, 2002

Health Maintenance

- **No assumption about a woman's health care needs should be based on the nature and extent of her disability**
- **We can't afford to be naïve about sexual abuse, exposure to disease, and pregnancy in special needs populations**

Breast Health

- **Considerations**

- Family history
- Living environment - residential or home care

- **Breast exams**

- Monthly “at home” exam; Annual physician exam
- Signs of problem
 - Lump or hard, flat area on breast
 - Nipple changes and/or discharge
 - Change in size, contour, texture, or temperature
 - Swelling in armpit

Gynecological Exams In Special Populations: *a conundrum*

- Disability protections that all individuals should be treated equally
- Necessity of pelvic exam versus possible trauma
- Reasons for exams
 - Excessive or absent bleeding – anatomical
 - Pain
 - Sexual Abuse
 - Infections - yeast and sexually transmitted diseases
 - Cancer
- Type and frequency of pelvic exam
controversial

The Gynecological Exam

Responsibilities

- ***Parents*** - give a thorough and accurate history
- ***Physician*** – perform the most thorough exam with sensitivity and that addresses the symptoms
- ***Both*** – give explanation and support
 - Don't forget to talk TO the woman before and during
 - Consider sedation
- **Recto-abdominal bimanual and cervical exam at age 21 and every 2 years or as symptoms change**
 - Blind brush cervical smear less traumatic
 - Various positions can be used besides “stirrups”

RETT WOMANHOOD and AGING...

Accentuate the POSITIVE

- Scoliosis risk lessens
- Social skills and interaction improve
- “Rett Behaviors” diminish
- EEG may become more normal - seizures may occur less often or disappear
- Breathing irregularities may decrease
- Physical maturity is a NORMAL process

Rett Syndrome World Congress

Family and Scientific Conference

June 22-25, 2012

New Orleans, Louisiana - USA

www.rettsyndrome.org

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