Dysfunctional Uterine Bleeding (DUB)

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DUB: **definition**, mechanism of normal menses, causes and classification

**Anovulatory DUB:** Etiology, pathophysiology, pathological change, diagnosis, differential diagnosis, diagnostic methods, treatment (principle)

**Ovulatory menstrual dysfunction:** classification, diagnosis, differential diagnosis, diagnostic methods, treatment
Abnormal uterine bleeding with no organic causes

what’s normal menstruation?
what’s meaning of the “no organic causes”?

A diagnosis of exclusion
Normal Menses

Cycle: a range of 21 to 35 days,
Duration: 2~8 days
Average blood loss: 20~60ml.
Endocrine and endometrial change in menstrual cycle

Changing hormone levels during the menstrual cycle.
Normal menses
The shedding of the decidua functionalis
### Terminology of abnormal menses

<table>
<thead>
<tr>
<th>Term</th>
<th>Interval</th>
<th>Duration</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menorrhagia</td>
<td>Regular</td>
<td>Prolonged</td>
<td>Excessive</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>Irregular</td>
<td>prolonged</td>
<td>Normal</td>
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<tr>
<td>Menometrorrhagia</td>
<td>Irregular</td>
<td>Prolonged</td>
<td>Excessive</td>
</tr>
<tr>
<td>Polymenorrhea</td>
<td>Frequent,</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>regular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomenorrhea</td>
<td>Regular</td>
<td>Normal</td>
<td>Less</td>
</tr>
<tr>
<td>Intermenstrual bleeding</td>
<td>Occurs between</td>
<td>bleeding</td>
<td>otherwise</td>
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<tr>
<td></td>
<td>bleeding</td>
<td>otherwise</td>
<td>normal</td>
</tr>
<tr>
<td></td>
<td>normal</td>
<td>menstrual</td>
<td>cycles</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>Infrequent,</td>
<td>Variable</td>
<td>Scanty</td>
</tr>
<tr>
<td></td>
<td>irregular</td>
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DUB Causes

Malnutrition
Emotional change
Endocrine disease, etc.

Dysfunction of Hypothalamic-pituitary-ovarian axis (HPO axis)

DUB
Classification

- 70~80% **Anovulatory DUB**
  most in puberty and menopausal transition period

- 20~30% **Ovulatory menstrual dysfuction**
  most in reproductive age
Contents

**DUB**: definition, mechanism of normal menses, causes and classification

Anovulatory DUB: Etiology, pathophysiology, pathological change, diagnosis, differential diagnosis, diagnostic methods, treatment (principle)

Ovulatory menstrual dysfunction: classification, diagnosis, differential diagnosis, diagnostic methods, treatment
A 17-year-old girl, Amenorrhea for 4 months,
First 5 days drop bleeding, with subsequent heavy bleeding for 7 days,
Short of breath, pale,
Bp: 80/50mmHg, Hb: 50g/L

Diagnosis? Any other examinations needed?
Treatment?
Etiology of Anovulatory DUB

1. Puberty

Immaturity of HPO axis

↓

Low FSH and LH

↓

Anovulation

↓

Persistent E2
No Progesterone
2. Menopausal Transition Period

Ovarian failure, follicle reduced

↓

Insensitive to FSH and LH, low estrogen

↓

Anovulation

↓

Persistent E2

No Progesterone
Pathophysiology

Persistent E2, Absence of P → Endometrial hyperplasia

Breakthrough bleeding

Low E2—irregular and prolonged bleeding

High E2—amenorrhea followed by acute and heavy bleeding

Withdrawal bleeding

Follicle atresia--
Dysfunction of self-limiting mechanism of menstruation

Fragile endometrium (lack of stromal support)

Irregular shedding

Abnormal vascular structure and function

Dysfunction of coagulation and fibrinolysis

Disorder of vascular factors (PGE2 ↑↑)
Pathological change

1. Proliferative phase endometrium

2. Endometrial hyperplasia (simple, complex, atypical)

3. Atrophic endometrium

Based on “architectural and cytologic features”
Simple hyperplasia

Architectural:
Dilated or cystic glands,
Slightly irregular shapes,
No glandular crowding

Increased glandular-to-stromal ratio

Cytologic:
No cytologic atypia

Progression to cancer: 1%
Complex hyperplasia

**Architectural:**
Complex (budding and infolding)

Crowded glands with less intervening stroma

**Cytologic:**
Without atypia

Progression to cancer: 3%
Atypical hyperplasia

Architectural:
Simple or complex

Cytologic: Atypia
1. Large nuclei of variable size and shape that have lost polarity
2. Prominent nucleoli
3. Irregularly clumped chromatin
4. Increased nuclear-to-cytoplasmic ratios

Progression to cancer: 23%

Not DUB, organic disease

1884

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Theories of development of Type I endometrial cancer

Chronic Oestrogen Overstimulation

- Normal endometrium
  - Simple hyperplasia
  - Complex hyperplasia
  - Atypical hyperplasia
  - Endometrial cancer
  - Kurman 1984

Genetic hit with clonal expansion

- Chronic Oestrogen Overstimulation
  - Genetic hit
  - Estrogen

Proliferative Endometrium

- Endometrial Intraepithelial Neoplasia
  - Endometrial Cancer

Benign Reactive Hyperplasia

- Mutter 2000
Diagnosis

Medical history
Physical examination
Laboratory tests
Imaging tests

A diagnosis of exclusion
Differential diagnosis

All diseases resulting in irregular vaginal bleeding should be excluded

- Pregnancy related disease
- Reproductive tumor
- Infection
- Trauma
- Hormone therapy & IUD
- Systemic disease (ITP etc.)
<table>
<thead>
<tr>
<th>Cause of bleeding by approximate frequency and age group</th>
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<tbody>
<tr>
<td><strong>Adolescent</strong></td>
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<tr>
<td><strong>Anovulation</strong></td>
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<tr>
<td><strong>Exogenous hormone use</strong></td>
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<tr>
<td><strong>Pregnancy</strong></td>
</tr>
<tr>
<td><strong>Coagulopathy</strong></td>
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Diagnostic methods

● **Medical history**
  
  Symptoms
  Contraception methods
  Medicine history (hormone therapy)
  Systemic disease (liver disease, hematological disease, thyroid disease)
Physical examination

Systemic examination

A complete pelvic examination--- to rule out organic causes

( eg. Cervix cytology : to rule out cervical cancer)
Initial Lab tests and Imaging tests

1. HCG to rule out pregnancy
2. A complete blood count with platelets
3. Blood coagulation tests (PT, APTT, Fbs)
4. Ultrasonography

How severe her anemia is?
Coagulopathy?
Further inspections

4. Hormone test
   (FSH, LH, E2, PRL, T, PRL, TSH, FT3, FT4)
5. Cervical mucus

Is this case an anovulatory DUB or ovulatory DUB?
6. BBT (basal body temperature)

Is this case an anovulatory DUB or ovulatory DUB?

Normal BBT
7. MRI if necessary

8. Endometrial sampling
   - Dilation and curettage, D & C
   - Endometrial biopsy

9. Hysteroscopy
Treatment

Nonsurgical management

Surgical treatment
Non surgical management

**Medicine for hemostat:**
- **Hormone therapy**, NSAIDs, Antifibrinolytics

**Treatment of anemia**
- Vitamin C, iron supplements, blood transfusion

**Prevent infection**
- Antibiotics

**Nutrition**
Medication: First line therapy

Principle – very important

1) Hemostasis
2) Regulating menstrual cycle

3) Prompting ovulation
3) Preventing cancer

Reproductive age
Menopausal transition period

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Step 1: Hemostasis

Mild bleeding: use lowest dose of hormone

Acute heavy bleeding: use high dose hormone

take effect in 6~8h,
stop bleeding in 24~48h
if >96h bleeding continues, reevaluated
the patients, "organic diseases"?
1. **high dose estrogen**: to stop heavy bleeding in anovulatory DUB in adolescents and reproductive age patients

**Conjugated estrogen**
- 2.5mg q6h

**Heavy bleeding**
- Day begin therapy
- 1
- 2.5mg q8hX3d
- 2.5mg q12hX3d
- 1.25mg q8hX3d
- 1.25mg q12hX3d
- 1.25mg qd

**Withdrawal bleeding**
- Hb>90g/L, add Progestin X10d

**Contraindications**: thrombus, coagulation diseases
2. (1) Progesterone in second half of the cycle “medication curettage”

For patients with moderate level of estrogen, Hb>80g/l, vital signs stable
Convert proliferative endometrium to secretion phase

Progesterone used in Second half of the cycle—mild bleeding
(2) Progesterone in whole cycle

For heavy bleeding with moderate E2

norethindrone
5mg q6h until bleeding stops

5mg q8hX3d
5mg q12hX3d
3.75mg q12hX3d
5mg qdX11d

Heavy bleeding

Stop bleeding

Withdrawal bleeding

Day begin therapy
1 3 6 9 12 15 18 23

Stop bleeding
1 20
3. Combined estrogen and progesterone (Oral Contraceptive)

Mild bleeding
Diane-35, Marvelon, Minulet
1# qd for 21d, 3-6 months

Heavy bleeding
Diane-35, et al 1~2 # q6h/q8h
reduce dose 1/3 every 3d→1# qd for 21d
4) **Androgen**: anti-estrogen effect

5) **Levonorgestrel-releasing IUD**: reduce 80-90% of total bleeding
Medication: First line therapy

Principle – very important

1) Hemostasis
2) Regulating menstrual cycle
3) Prompting ovulation
3) Preventing cancer

Reproductive age
Menopausal transition period
Step 2: Regulating menstrual cycle

For adolescents and reproductive patients:
To restore the H-P-O function

For peri-menopause patients:
To control the volume and prevent endometrial hyperplasia
1. Sequential E-P therapy (artificial cycle)

For adolescents and reproductive patients with low level estrogen
2. Oral contraceptives (E+P combined therapy)

for patients in reproductive period with high level estrogen and perimenopausal patients

Day begin therapy

1

Menstrual cycle

5

Contraceptives

21

Withdrawal bleeding

26
3. Progesterone used in second half of the cycle for adolescents and peri-menopausal patients.

- Day begin therapy
- Bleeding
- Menstrual cycle 5
- Progesterone
- Withdrawal bleeding
- 1 Day
- 1, 10
- 16
- 25
Medication: First line therapy

Principle—very important

1) Hemostasis
2) Regulating menstrual cycle

3) Prompting ovulation
3) Preventing cancer

Reproductive age
Menopausal transition period
Step 3: Prompting ovulation

for reproductive age patients desire for birth

- Mostly, spontaneous ovulating begins as soon as the sequential and combined E-P therapy stops
- Not recommended for adolescents
- For those failed the therapy: Clomiphene citrate, HMG, HCG et al
Step 3   Prevent cancer

For patients who had long history of anovulation

1. Surgical treatment
   1) D & C
      Objective: hemostasis & diagnosis
      ◆ >35 years old, but not limited to these women
      ◆ Ineffective to medicine
      ◆ Risk for endometrial cancer

2) Endometrial ablation (hysteroscopy)
3) Hysterectomy
2. Hormone therapy:

1) Oral contraceptive

2) Progesterone used in second half of cycle — simple hyperplasia

3) Progestrone used in whole cycle — complex hyperplasia
Summary: hormone therapy for A-DUB

1. Hemostasis
   1) E  2) P  3) E+P, E+P+T  4) T  5) IUD-P  6) other

2. Regulating menstrual cycle
   1) Sequential E-P therapy
   2) E+P combined therapy
   3) Progesterone used in Second half of the cycle

3. promote ovulation or prevent cancer
   1) CC  2) HMG  3) HCG or  1) surgery  2) P
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Ovulatory menstrual dysfunction

Classification

• **Menorrhagia:**

• **Intermenstrual bleeding**

  Peri-ovulation bleeding
  
  Luteal dysfunction
  
  Luteal phase defect, LPD
  
  Irregular shedding of endometrium
Menorrhagia

Regular period, normal duration, **excessive bleeding >80ml**
Normal endometrium, normal hormone level

**Mechanism:** increased fibrinolysis, prostglandins inbalance

**Treatment:** anti-fibrinolytics, OC, levonorgestrel-releasing IUD, P-whole cycle
1. Luteal Phase Defect, LPD

Causes:

- Low FSH--Dysplasia of the follicles
- Insufficiency of the LH peak
- Defects in the lower LH impulse after LH peak
- Hyperprolactinemia
- LH receptor defect of granulose cell
Pathology

Secretory endometrium:
- Inadequate Glands secretion
- No obvious Stroma edema
- Gland and stroma not comparable

Mechanism
- Not adequate progesterone production,
- Quick regression of the corpus luteum

Short secretory phase

Symptoms
- Polymenorrhea
- Short high temperature phase in BBT <11d
- Infertility or loss of early pregnancy
Diagnosis of LPD

1. Clinical symptoms

2. BBT, high temperature phase <11d

3. Endometrial biopsy: secretion later than 2 days
**LPD Treatment**

**Stimulating follicular development**
CC 50mg/day for 5 days from 1st day

**Enhancing the LH peak**
HCG 5,000 or 10,000IU when the follicles are mature

**Stimulating luteal function**
HCG for 5 days during luteal phase

**Replacement therapy**
Progesterone 10mg for 10-14 days in luteal phase

**Hyperprolactinemia**
Bromocriptine 2.5-5.0mg/d
2. Irregular shedding of endometrium

Normal Ovulation
Normal Luteal development
Uncompleted regression of the corpus luteum
Mechanism
Persistent progesterone’s effect
Incomplete shedding of endometrium

Pathology
Secretory endometrium on the 5th day

Symptoms
Prolonged menstruation 9-10 days
Regular cycle
Heavy bleeding
Diagnosis of irregular shedding of endometrium

1. Prolonged menstruation
2. High temperature presents slow returning to the lower temperature phase
3. Biopsy at 5th day: secretory endometrium
Normal BBT
Treatment of irregular shedding of endometrium

1. Stimulating luteal function
   HCG for 5 days during luteal phase

2. Replacement therapy
   Progesterone 10mg for 10-14 days in luteal phase

3. OC
A 17-year-old girl, amenorrhea 4 months
First 5 days drop bleeding, with subsequent heavy bleeding for 7 days,
Short of breath, pale,
Bp: 80/50mmHg, Hb: 50g/L

Diagnosis?
Additional lab tests or check-up?
Differential diagnosis?
Treatment?
Thank you!