ΛΕΙΤΟΥΡΓΙΚΗ ΑΙΜΟΡΡΑΓΙΑ ΤΗΣ ΜΗΤΡΑΣ ΣΤΗΝ ΕΦΗΒΕΙΑ

Γ ΚΡΕΑΤΣΑΣ MD FACS FRCOG FACOG

ΜΑΙΕΥΤΗΡΙΟ «ΜΗΤΕΡΑ»

ΑΘΗΝΑ 22 ΦΕΒΡΟΥΑΡΙΟΥ 2007

- **MENSTRUAL DISTURBANCES 60% FOR THE FIRST (2) GYNECOLOGICAL YEARS**
- **OLIGOMENORRHEA**
- **DUB**
- **DYSMENORRHEA**

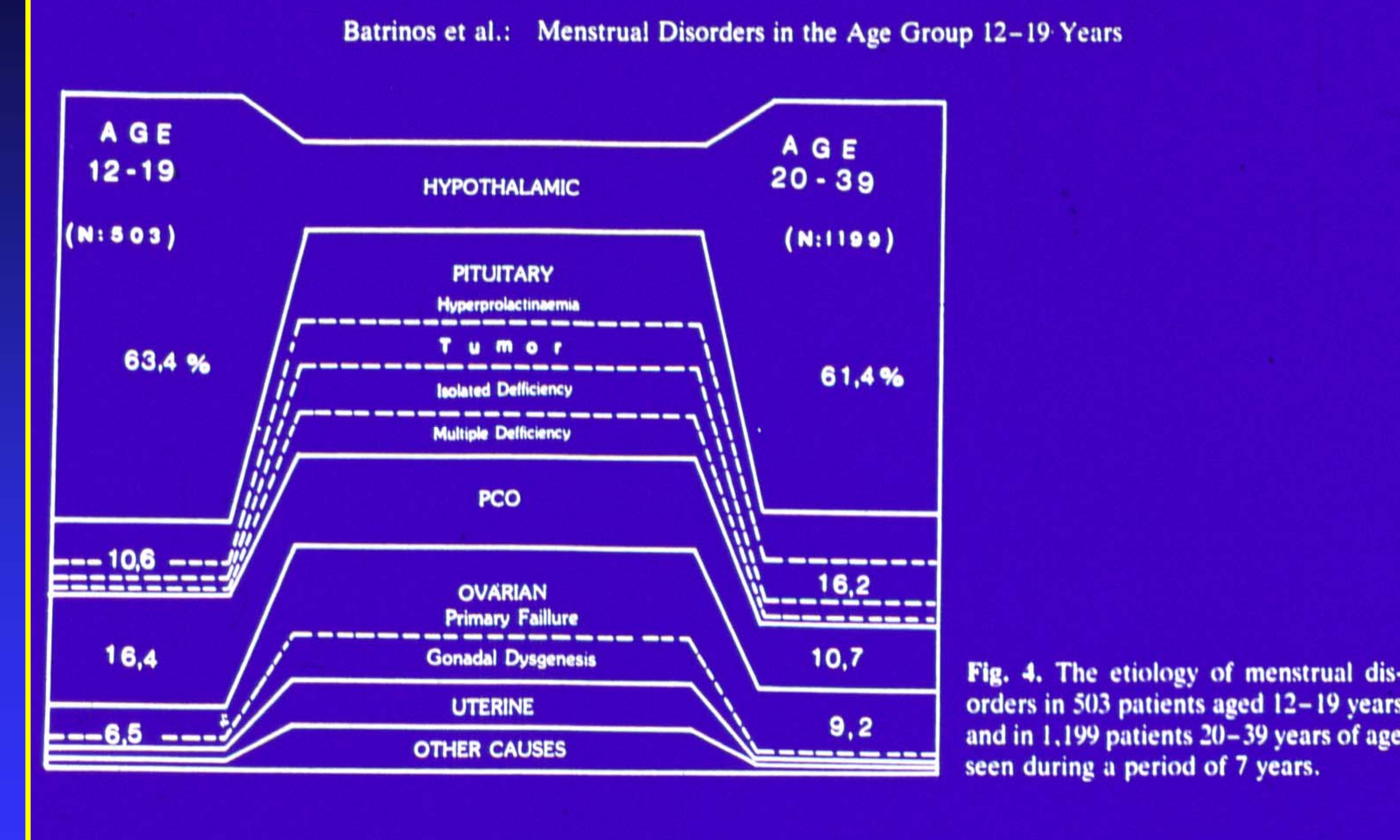


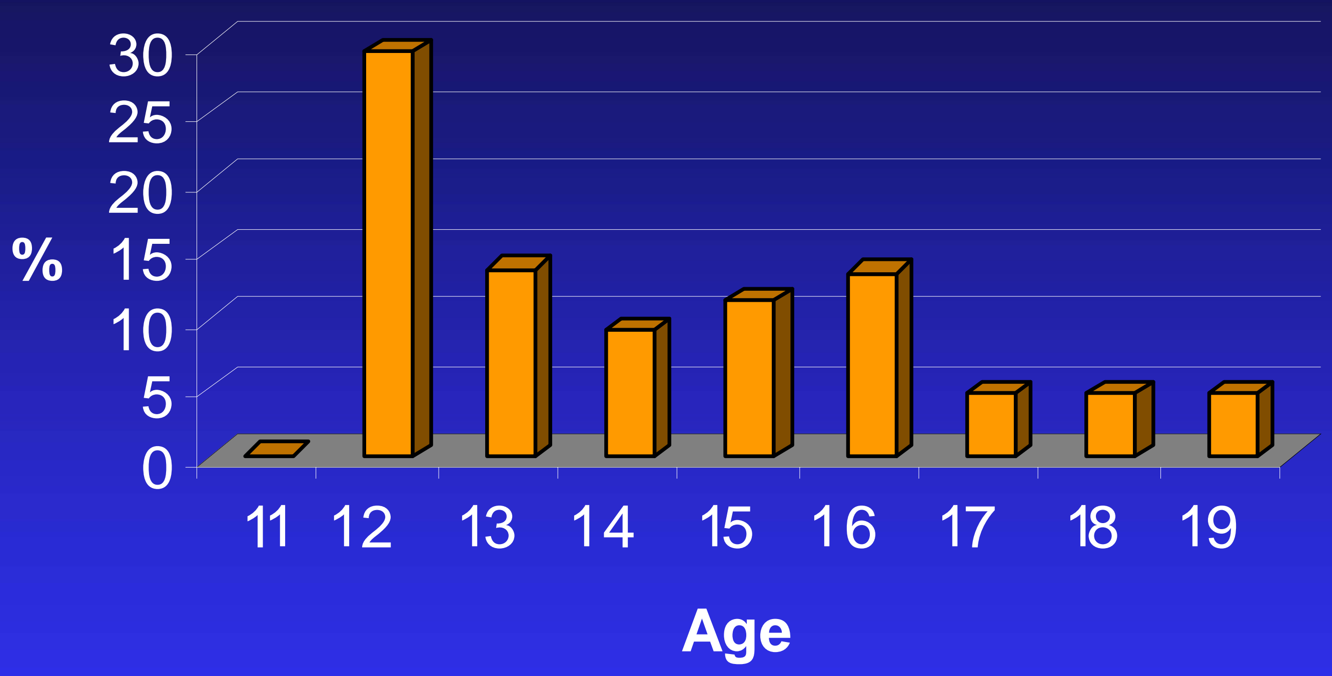
Fig. 4. The etiology of menstrual disorders in 503 patients aged 12–19 years and in 1,199 patients 20–39 years of age seen during a period of 7 years.

MENSTRUAL DISORDERS DURING ADOLESCENCE

Menstrual Disorder	Incidence %
DUB	381 (48.2%)*
• Amenorrhea	180 (22.8%)
• Oligomenorrhea	165 (20.9%)
• Dysmenorrhea	64 (8.1%)
TOTAL	790 Cases

University of Athens Medical School
2nd Dept of Ob/Gyn, 2004
Deligeoroglou E.,Christopoulos P., Delibelioti A.,

DUB AGE OF PATIENTS



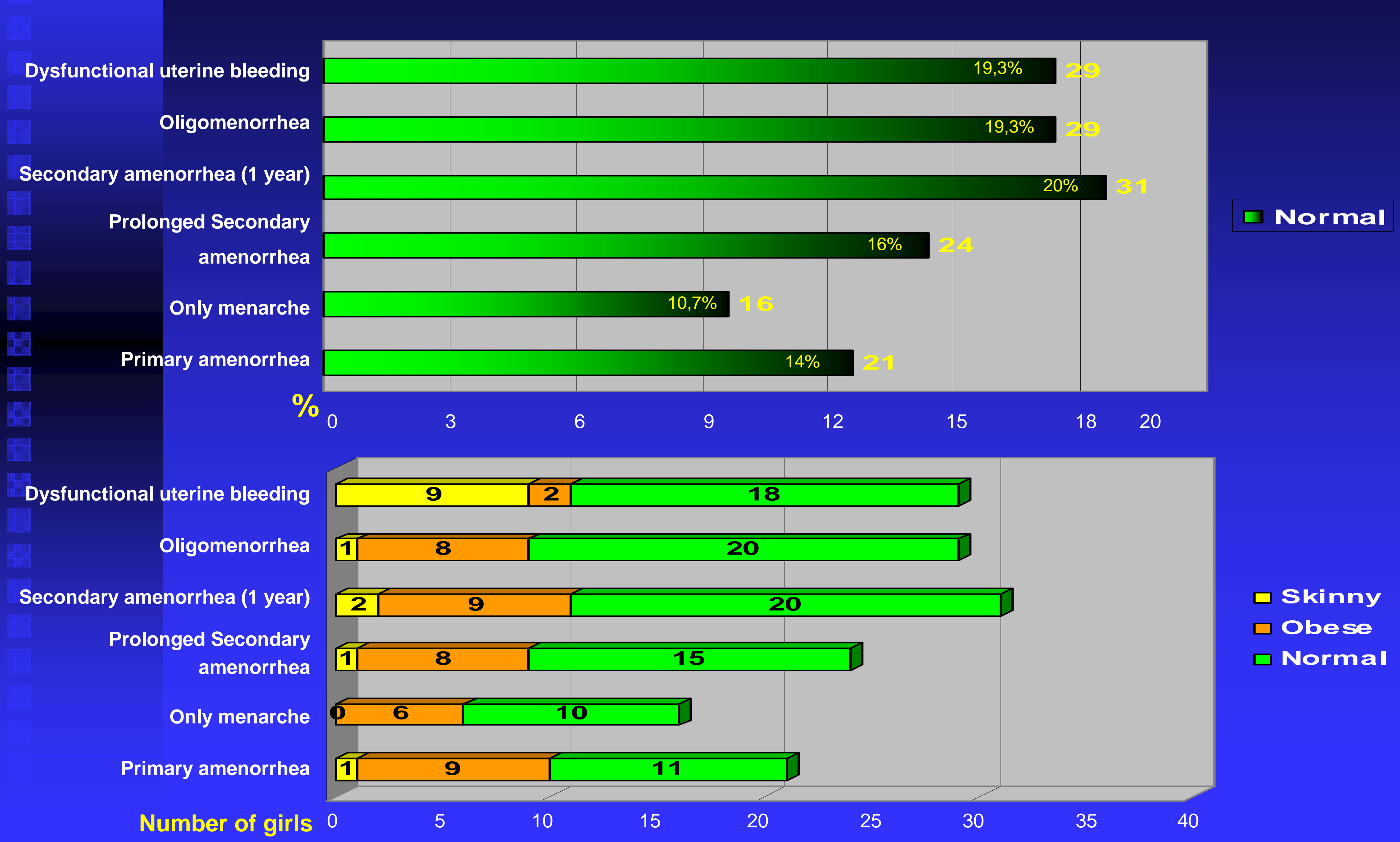
Univ of Athens Medical School

1 2nd Dept of Ob Gyn 2004

PCOs IN ADOLESCENTS

Types of menstrual disorder among PCOS patients (a)

Distribution of bodyweight by the type of menstrual disorder in PCOS patients (b)



PATIENT'S EVALUATION

- CLINICAL HISTORY
- GYNECOLOGICAL EX
- ULTRASONOGRAPHY
- ENDOCRINOLOGICAL PROFILE
- LAPAROSCOPY - HYSTEROSCOPY

PROPOSED MECHANISMS OF ENDOMETRIAL AUB DUE TO NON - ORGANIC CAUSES

- Hyperestrogenic or progestogenic state
- Abnormal neovascularization (angiogenesis)
- Increased enzymatic tissue/vascular breakdown
- Impaired hemostatic mechanisms

Ferenczy Maturitas 2003

ANGIOGENESIS IN THE FEMALE REPRODUCTIVE ORGANS: PATHOLOGICAL IMPLICATIONS

Reynolds LP et al Int J Exp Pathol 2002

- **The female reproductive organs are some of the few adult tissues that exhibit regular intervals of rapid growth**
- **They also are highly vascular and have high rates of blood flow**
- **Angiongenesis, or vascular growth, is therefore an important component of the growth and function of these tissues**
- **As with many other tissues, vascular endothelial growth factors (VEGFs) and fibroblast growth factors (FGFs) appear to be major angiongenic factors in the female reproductive organs**

continued

ANGIOGENESIS IN THE FEMALE REPRODUCTIVE ORGANS: PATHOLOGICAL IMPLICATIONS

- A variety of pathologies of the female reproductive organs are associated with distrurbances of the angiogenic process, including DUB, endometrial hyperplasia, carcinoma and endometriosis

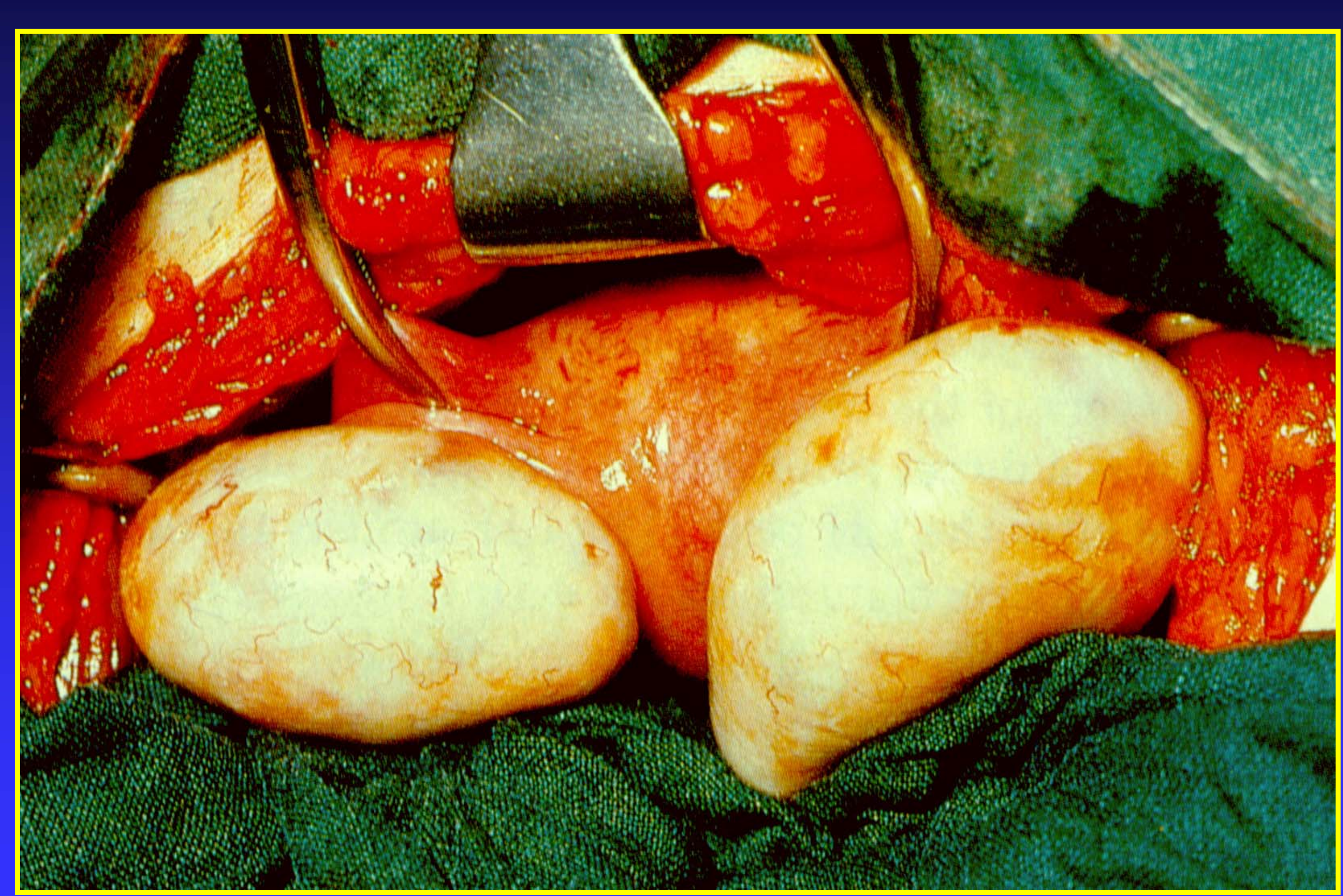
- In the near future, angiogenic or antiangiogenic compounds may prove to be effective therapeutic agents for treating these pathologies.

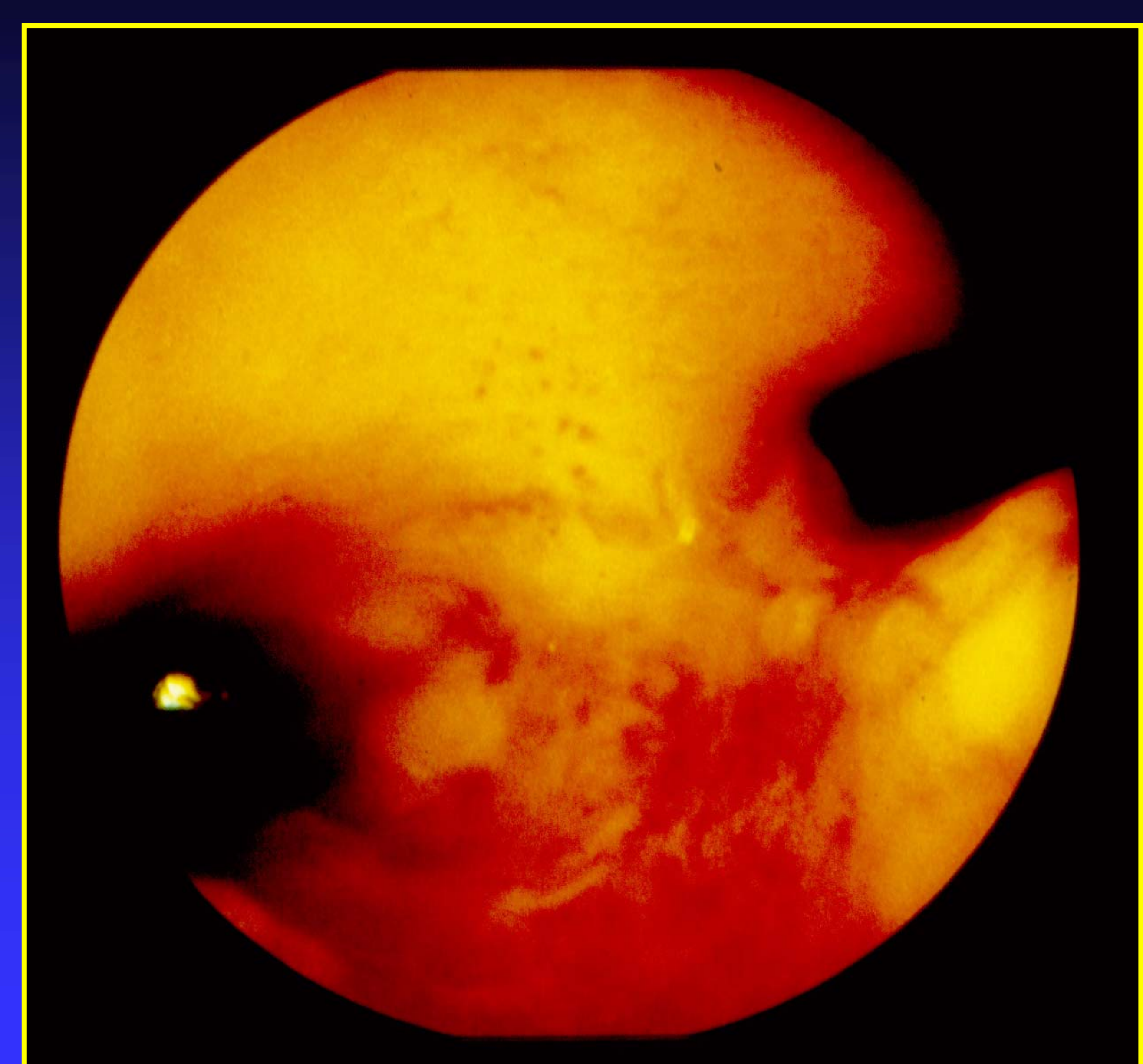
- Cycling endometrium requires repeated, rapid and short-term proliferation and equally rapid inhibition of neovascularization

- Endometrial angiogenesis is regulated by a myriad of growth factors and cytokines which in turn are influenced by levels of E_2 and P of the menstrual cycle

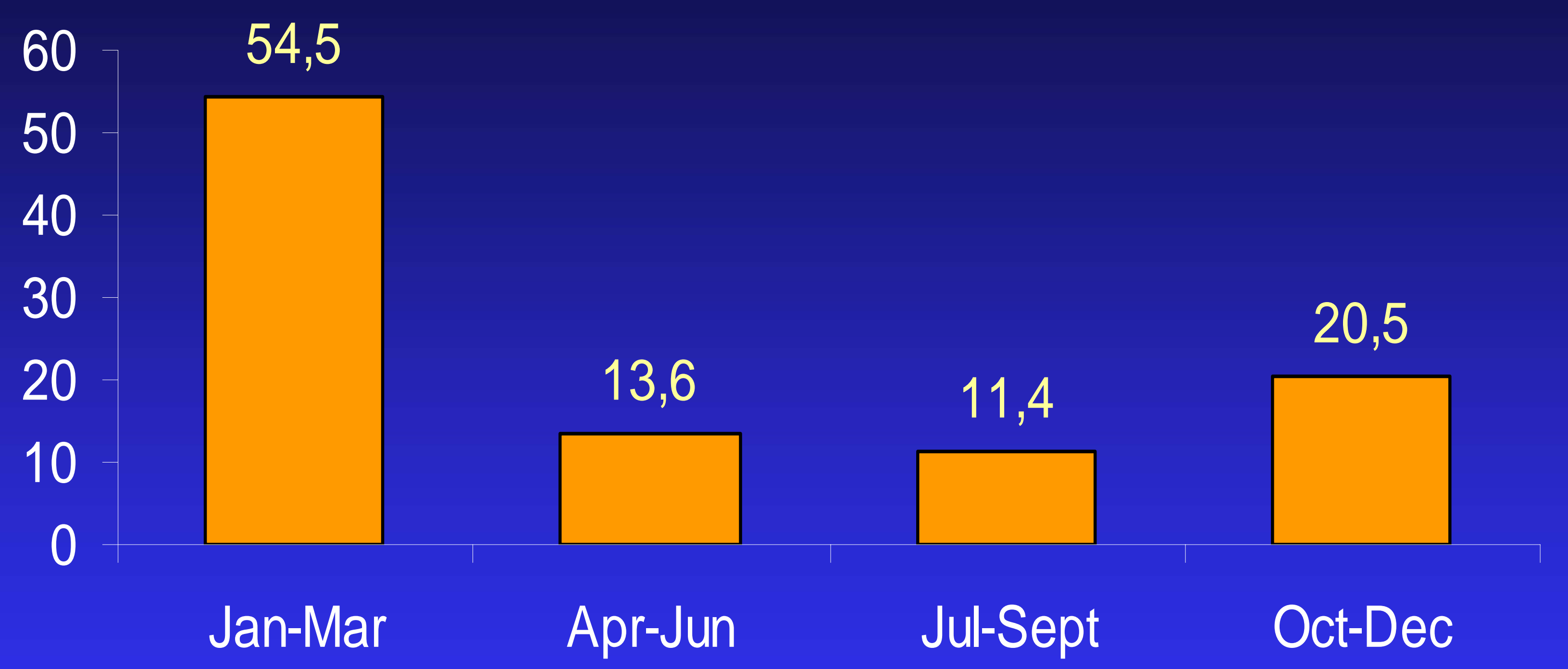
- Production of VEGF is stimulated in vitro by both E2 and progestogens and patients with LNG implants have increased levels of VEGF and endometrial capillary density

Endometrial Angiogenesis A. Ferenczy Maturitas 45 (2003) 1-14





SEASONAL DISTRIBUTION



University of Athens Medical School
2nd Dept of Ob/Gyn, 2004
Delibeoroglou E Christopoulos P Delibelioti A

DUB DIFFERENTIAL DIAGNOSIS

- PREGNANCY COMPLICATIONS
- NEOPLASMS OF THE GENITAL SYSTEM
- GENITAL TRACT INFECTIONS
- ENDOCRINOPATHIES
- TX DRUGS AND HORMONES
- TRAUMA
- COAGULATION DISORDERS
- CHRONIC SYSTEMIC ILLNESS

DUB DURING ADOLESCENCE CLINICAL GROUPING

- **GROUP 1. MILD HYPERMENORRHEA**

MP SLIGHTLY LONGER THAN NORMAL OR CYCLE SHORTENED FOR 2 OR MORE MONTHS HB AND HCT WITHIN NORMAL LIMITS

- **GROUP 2. MODERATE HYPERMENORRHEA**

MP MODERATELY PROLONGED CYCLE SHORTENED MODERATELY HEAVY FLOW HB 9-10gms NO SIGNS OF ANEMIA

- **GROUP 3. SEVERE HYPERMENORRHEA**

PROLONGED OR PROFUSED BLEEDING-MARKED ANEMIA WITH CLINICAL SIGNS HB LESS THAN 8gms

CLASSIFICATION OF 177 DUB CASES

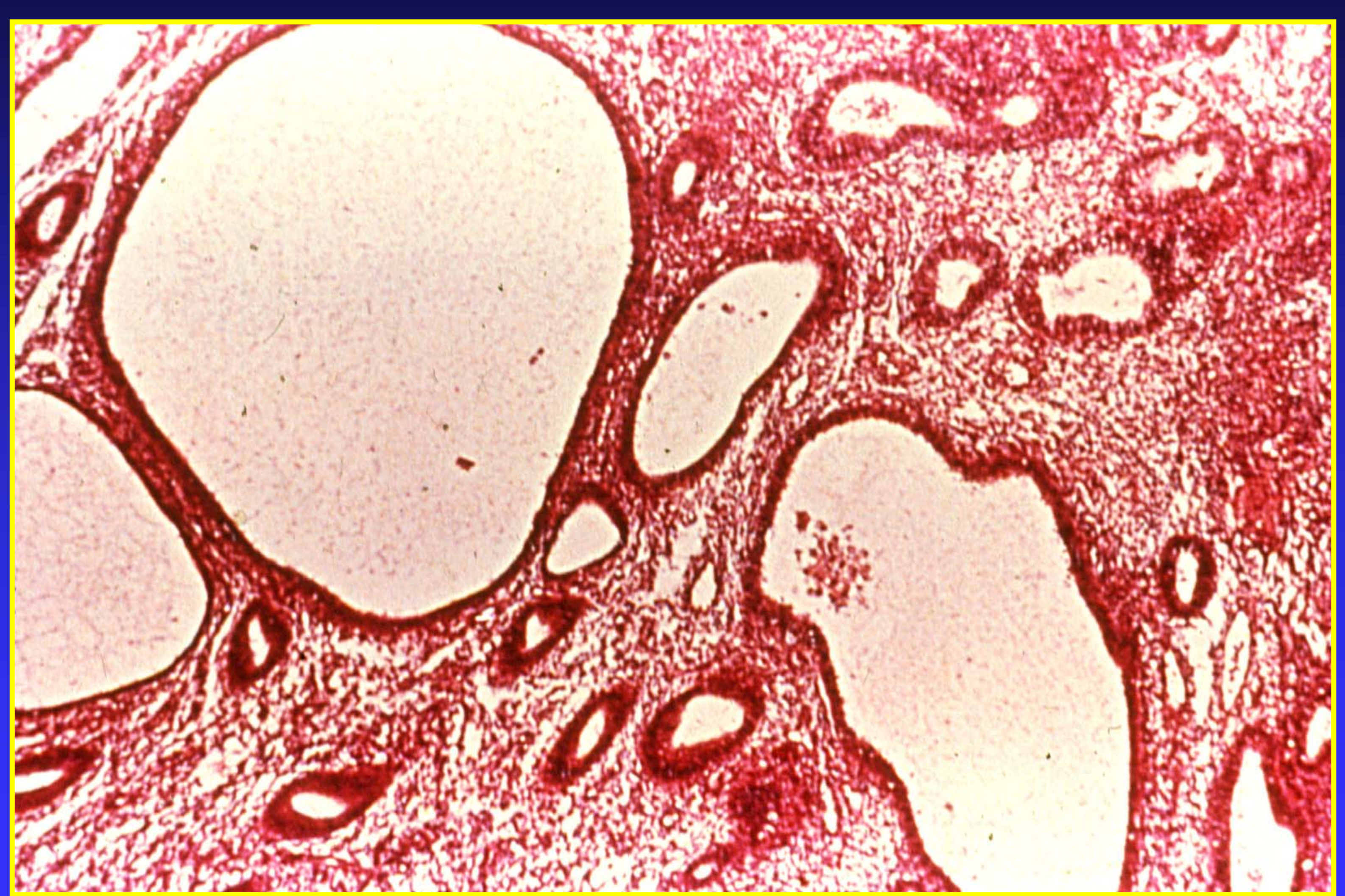
- 141 SEVERE
- 24 MODERATE
- 12 MILD

PATHOPHYSIOLOGY OF DUB

- ANOVULATION
- ABSENCE OF POSITIVE FEED BACK
- CONTINUOUS ESTROGEN SECRETION
- ENDOMETRIAL HYPERPLASIA
- INCREASED VASCULARITY
- LACK OF PROGESTERONE PRODUCTION
- ABSENCE OF STROMA STABILITY
- LACK OF PERIODIC VASOCONSTRICTION
- THE ROLE OF PROSTAGLANDINS
- ANGIOGENESIS

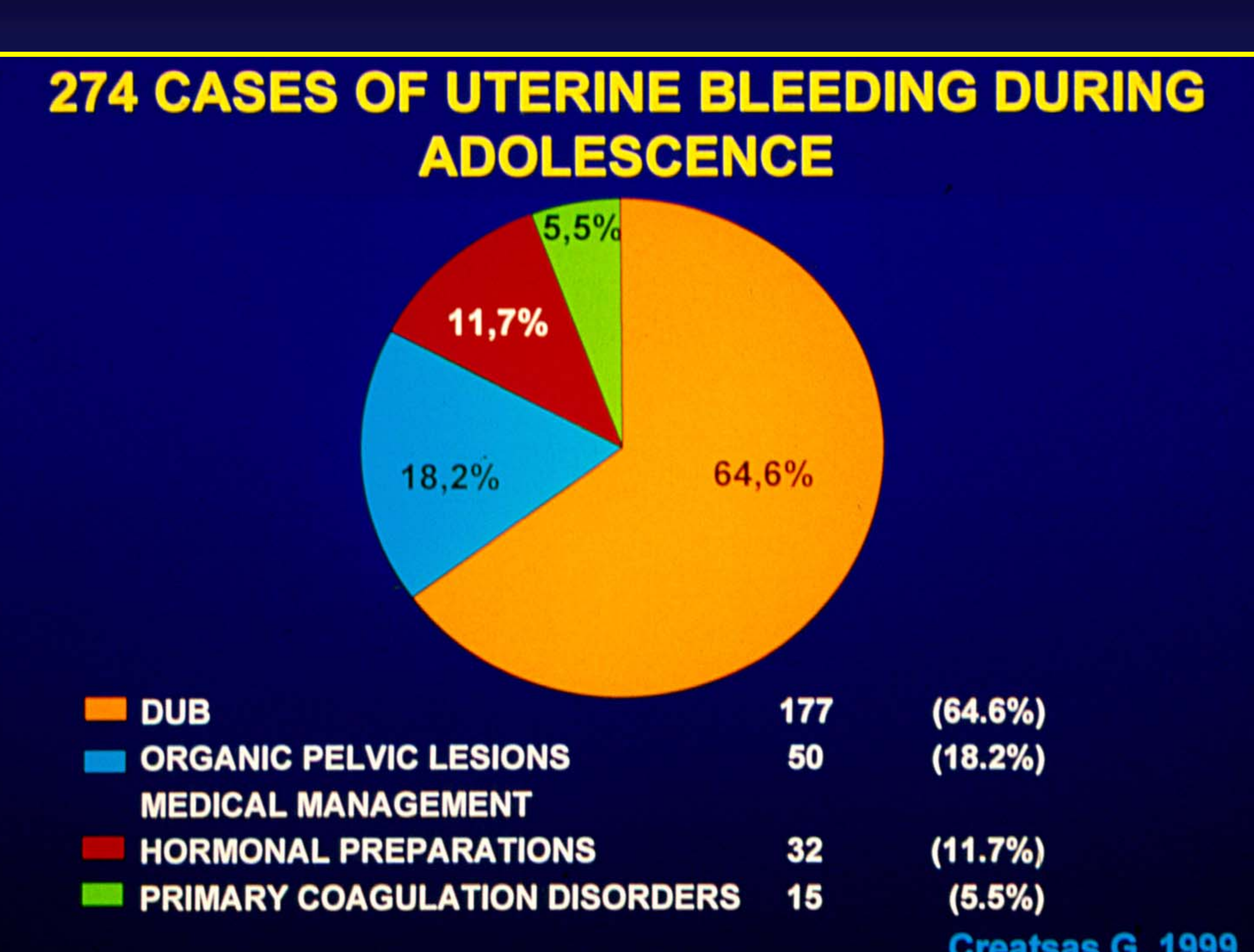
ENDOMETRIAL HISTOLOGY

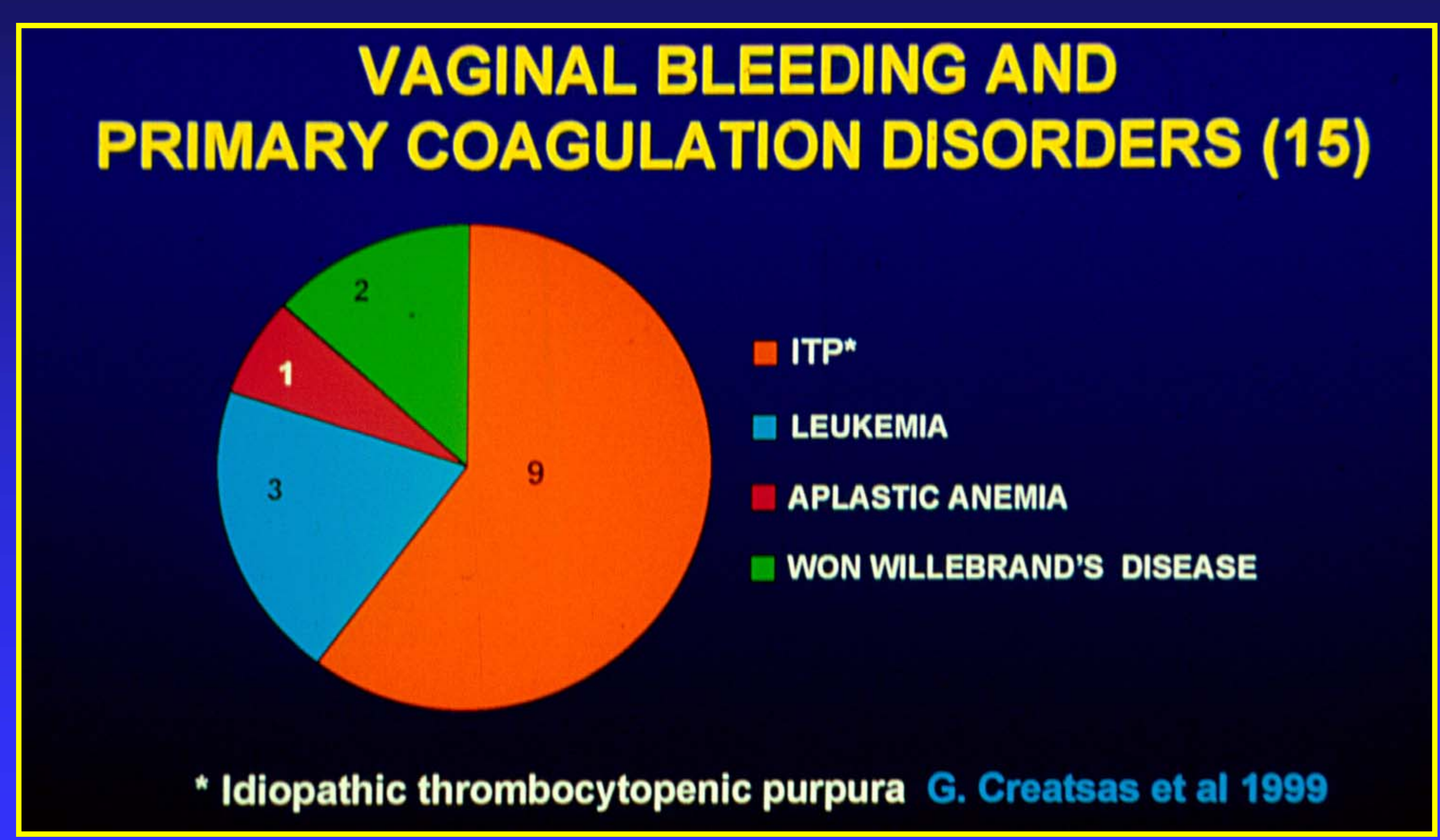
▪ HYPERPLASIA	54%
▪ PRODUCTIVE	4%
▪ SECRETORY	22%

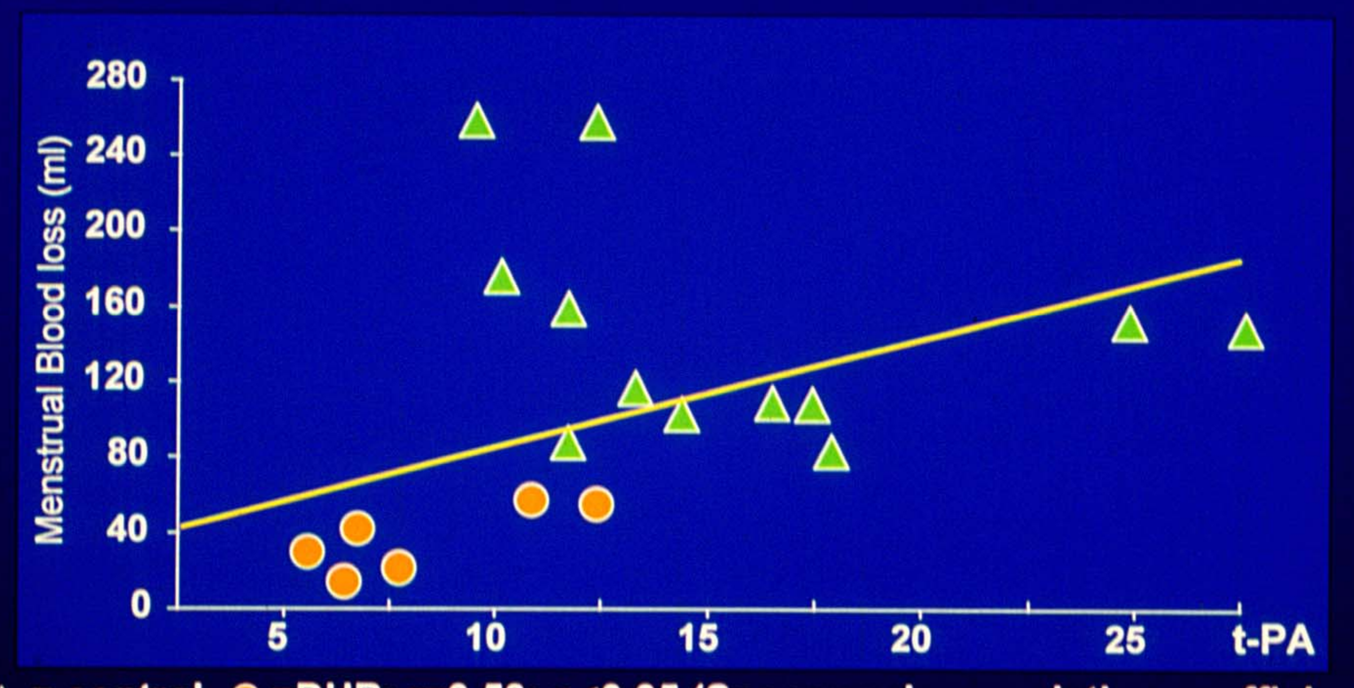


NON ORGANIC CAUSES OF DUB

A shift in the ratio of endometrial vasoconstrictor (PGF2-a) to vasodilator (PGE$_2$) and an increase in total endometrial prostaglandins have been demonstrated in ovulatory DUB patients


274 CASES OF UTERINE BLEEDING DURING ADOLESCENCE
5,5%
11,7%
18,2%
64,6%
DUB 177 (64.6%)
ORGANIC PELVIC LESIONS 50 (18.2%)
MEDICAL MANAGEMENT
HORMONAL PREPARATIONS 32 (11.7%)
PRIMARY COAGULATION DISORDERS 15 (5.5%)
Creatsas G. 1999


VAGINAL BLEEDING AND
PRIMARY COAGULATION DISORDERS (15)
2
1
3
9
ITP*
LEUKEMIA
APLASTIC ANEMIA
WON WILLEBRAND'S DISEASE
* Idiopathic thrombocytopenic purpura
G. Creatsas et al 1999



= control =DUB; r=0,53; p<0,05 (Spearman's correlation coefficient)

Gleeson et al 1993

SPECTRUM OF DYSFUNCTIONAL UTERINE BLEEDING AND ITS CONSERVATIVE MANAGEMENT

Siddiqui SH J Coll Physicians Surg Pak 2003

210 (16.1%) out of 1300 patients were diagnosed as having DUB. Response rate was 20-30% with oral mefenamic acid, 50% with capsules of tranexamic adic, 60% and 5% respectively with OC's containing EE and morethisterone or norethisterone alone

PATIENT SATISFACTION WITH THERMAL BALLOON ENDOMETRIAL ABLATION A RETROSPECTIVE REVIEW

Jarrell A, Olsen ME   J Reprod Med. 2003

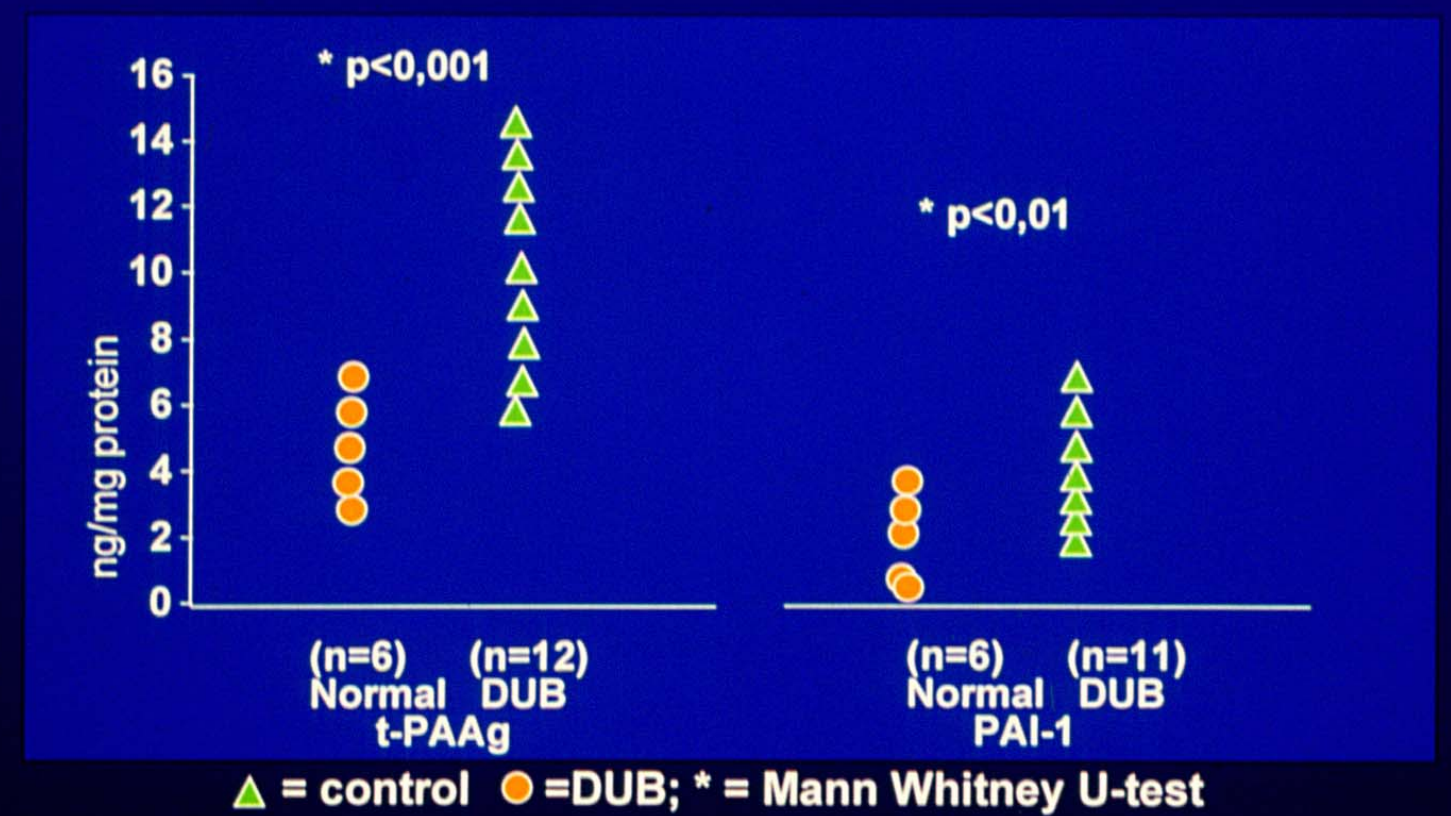
Less than 60% of women reported satisfaction with balloon endometrial ablation, and 40% underwent hysterectomy within 1 year year of it.

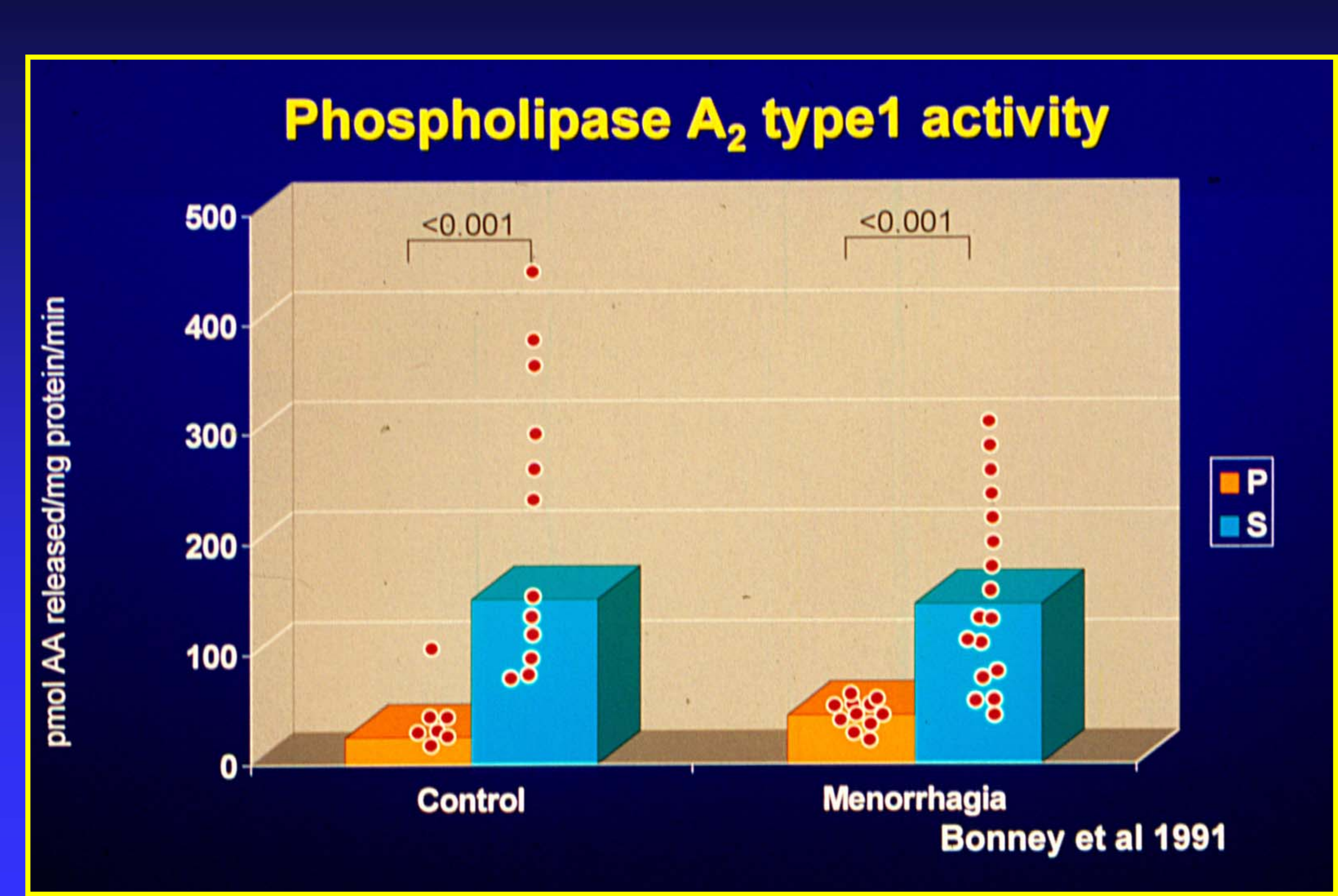
ROLE OF PROGESTERONE ANTAGONISTS AND NEW SELECTIVE PG RECEPTOR MODULATORS IN REPRODUCTIVE HEALTH

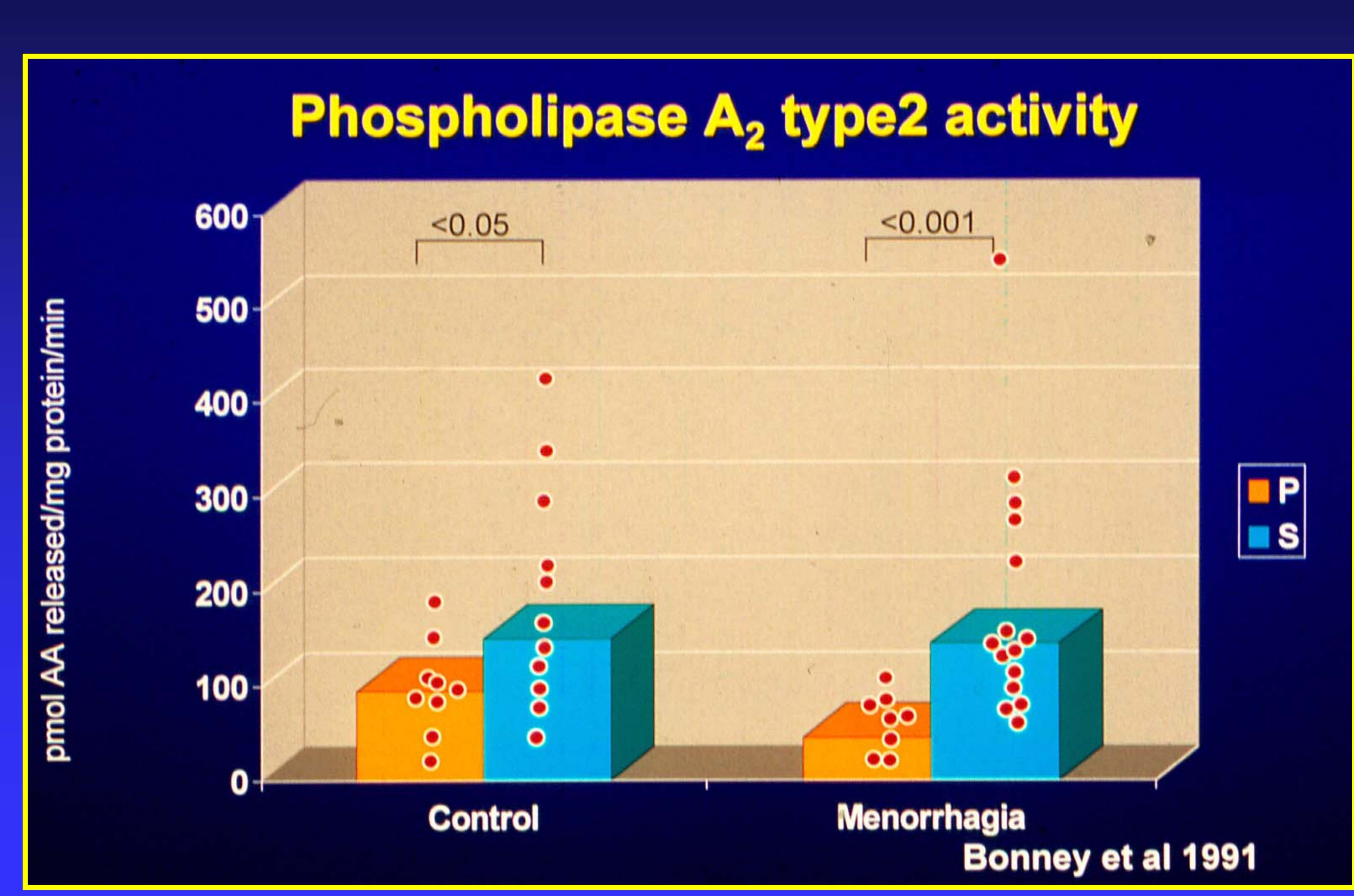
Olive DL, Obstet Gynecol Surv 2002

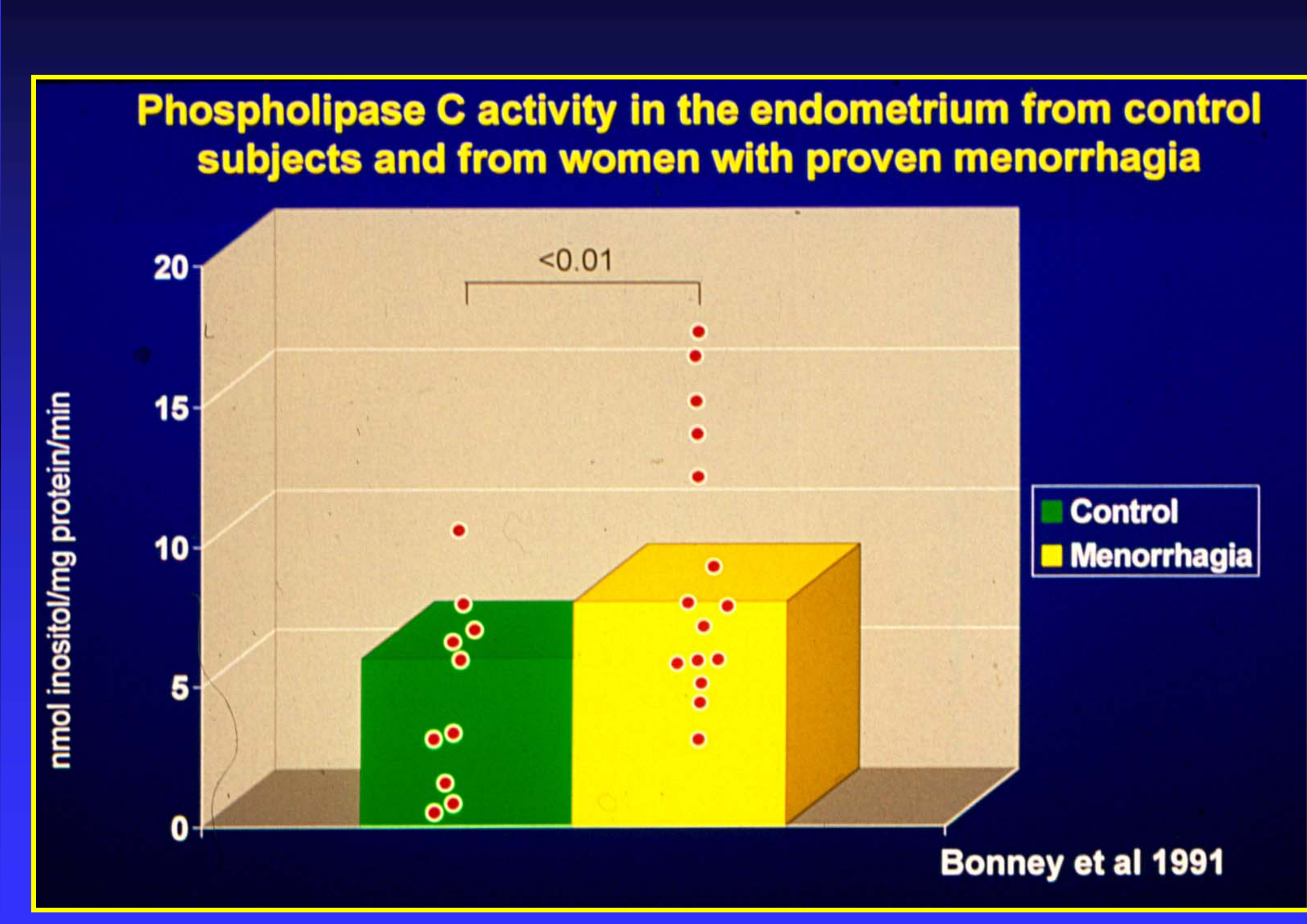
- **The selective PG receptor modulators (SPRMs) have both agonist and antagonist activities depending upon the site of action. These compounds have been studied for their effect on endometrial growth**
- **Endometrial vascular development**
- **TOP**
- **Induction of labor, the TX of endometriosis**
- **Fibroids**
- **Contraception**
- **DUB**

Tissue plasminogen activator antigen (t-PAAg) and tissue plasminogen activator inhibitor Type 1 (PAI-1) in menstrual endometrium in women and dysfunctional uterine bleeding

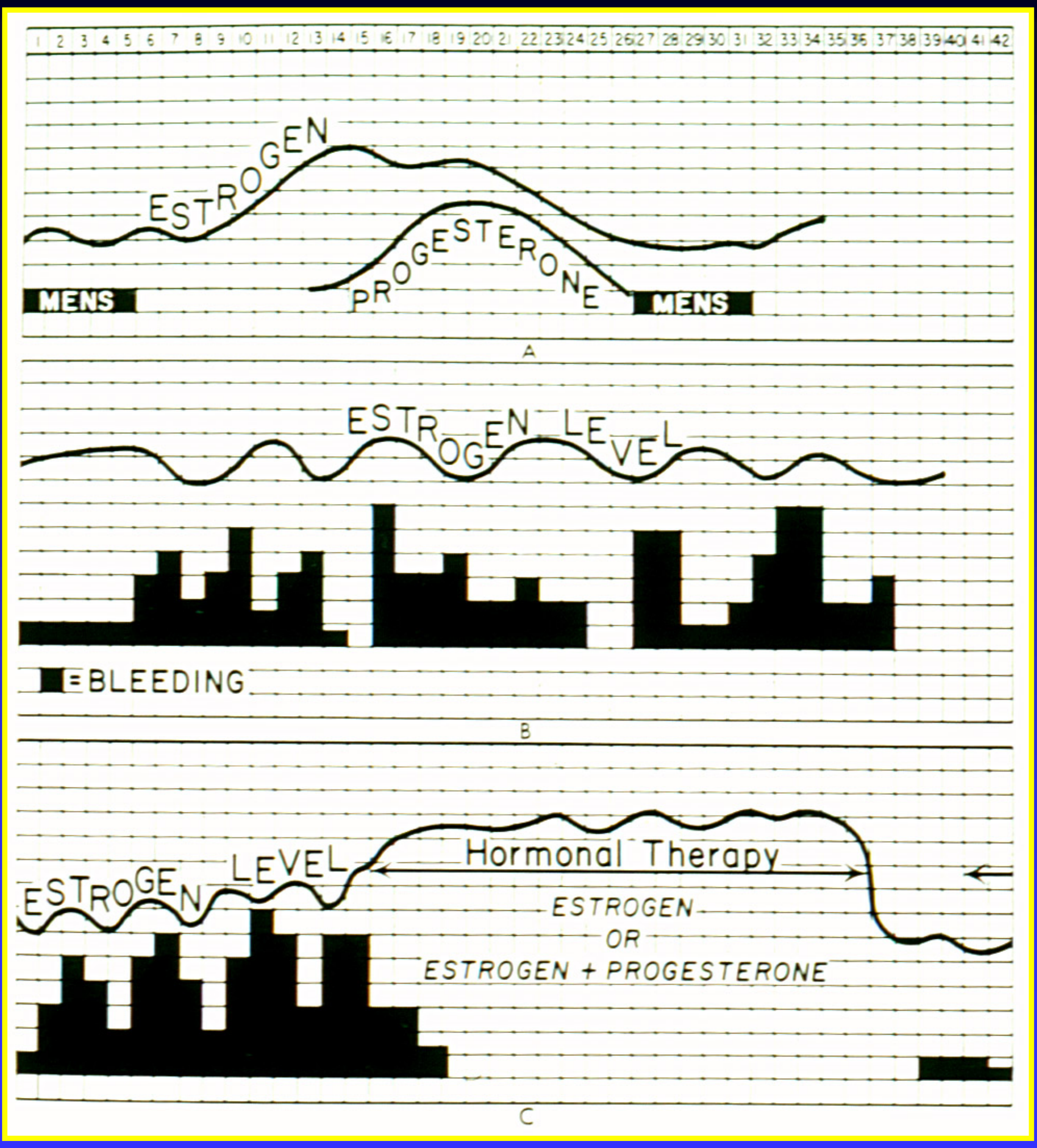



Phospholipase A2 type1 activity
pmol AA released/mg protein/min
500
400
300
200
100
0
<0.001
<0.001
P
S
Control
Menorrhagia
Bonney et al 1991


Phospholipase A2 type2 activity
pmol AA released/mg protein/min
600
500
400
300
200
100
0
<0.05
<0.001
P
S
Control
Menorrhagia
Bonney et al 1991



Phospholipase C activity in the endometrium from control subjects and from women with proven menorrhagia
<0.01
20
15
10
5
0
nmol inositol/mg protein/min
Control
Menorrhagia
Bonney et al 1991



1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42
ESTROGEN
PROGESTERONE
MENS
MENS
A
ESTROGEN LEVEL
= BLEEDING
B
ESTROGEN LEVEL
Hormonal Therapy
ESTROGEN
OR
ESTROGEN + PROGESTERONE
C

CHRONOLOGY OF STOP- DUB

Event	Date
STOP- DUB start	September 30, 1996
First full investigative group meeting	February 9-10, 1997
First clinical center certified	October 9, 1997
First randomized patient recruited	January 14, 1998
First DSMC meeting	February 13, 1998
Modification of primary outcomes by DSMC	February 13, 1998
First modification of sample size estimate presented to DSMC	July 29, 1998
Coordinating center and principal investigator move	September 30, 1998
Second modification of sample size estimate presented to DSMC	February 6-7, 1999
4-year results of Aberdeen study published	April, 1999
Replacement of DSMC members who resigned	February 23, 2000
Decision by steering committee to increase minimum length of follow-up to 4 years, funding permitting, and subsequent DSMC agreement	March 24, 2000

DSMC= Data and Safety Monitoring Committee

K. Dickersin et al. Controlled Clinical Trials 24 (2003) 591-609

STOP- DUB EXCLUSION AND PROVISIONAL ELIGIBILITY CRITERIA

A. Esclusion criteria for randomized trial an observational study

Prescreen

- Age < 18 years
- Postmenopause
- Bleeding not considered escessive by woman
- Desire to retain fertility
- Refusal to consider surgery
- Known myoma (from prior examination)

Eligibility screen

- Lack of willingness to have a gynecologic or ultrasound examination
- Lack of willingness to be interviewed about bleeding or consider study
- Pregnancy
- Prior endometrial resection or ablation
- Prior myomecomy myolysis or hysterectomy

continued

STOP- DUB EXCLUSION AND PROVISIONAL ELIGIBILITY CRITERIA

Medical history

- No tentative diagnosis of DUB
- History of malignancy of vagina, cervix, endometrium or ovary
- History of complex endometrial hyperplasia or simple hyperplasia with atypia
- Current use of tamoxifen
- <6 months since onset of excessive uterine bleeding[a]
- < 9 months since stopping the use of IUD[a]
- < 9 months since stopping the use of implantable hormone agent[a]
- < 18 months since stopping use of Dep- Provera[a]
- < 6 months of anovulatory DUB after reaching euthyroid status for woman with diagnosis of hypothyroidism[a]
- < 3 months since pathology results indicate presence of endometrial polyp[a]

continued

STOP- DUB EXCLUSION AND PROVISIONAL ELIGIBILITY CRITERIA

Baseline gynecologic examination

- **Enlarged (≥ 14 weeks gestational age) uterus**
- **Focal bleeding of genital, urinary, gastrointestinal tract**

Ultrasound examination

- **Presence of any submucosal myoma**
- **Presence of any myoma ≥ 3 cm, any location**
- **Presence of > 3 myomas, any size or location**
- **Presence of endometrial polyp(s)[a]**
- **Malignancy of the vagina, cervix, endometrium or ovary**

continued

STOP- DUB EXCLUSION AND PROVISIONAL ELIGIBILITY CRITERIA

Laboratory and ancillary tests

- FSH level in women ages ≥ 45 years confirming postmenopausal status
- Abnormal urinary tract or gastrointestinal tract imaging related to uterine bleeding
- Evidence of cervical cancer (screened by Pap smear in last 12 months and confirmed by colposcopy)
- Evidence of complex endometrial hyperplasia or simple hyperplasia with atypia or endometrial cancer (endometrial biopsy in last 12 months)
- Any test value consistent with a diagnosis of DUB
- Any test value, unlikely to change, compromising patient safety for surgery

continued

STOP- DUB EXCLUSION AND PROVISIONAL ELIGIBILITY CRITERIA

Other

- Any existing medical condition, unlikely to change, putting patient at excessive risk for surgery
- Request for prophylacic bilateral oophorectomy by women aged < 45
- Lack of willingness to comply with study requirements
- Uncooperative behavior
- Any coexisting condition that may influence a patient’s ability to comply with participation
- Refusal to allow evaluation or follow-up
- In process of scheduling surgery at time of baseline visit

* Patient may become eligible at later date

K. Dickersin et al. Controlled Clinical Trials 24 (2003)591-609

THE MANAGEMENT OF 177 DUB CASES

- ORAL CONTRACEPTIVES 43%
- CONJ. ESTROGENS AND PROGESTOGENS FOLLOWED BY OC'S 47%
- TRANSFUSION
- IRON SUPPLEMENTS
- REASSURANCE

TRIPHASIC NORGESTIMATE-ENTHINYL ESTRADIOL FOR TREATING DUB

Randomized double-masked study 201 women (15-50 years old)

Tx 3 consecutive cycles. Improvement more that 80% ($p<0.001$)

to controls (50%)

Godwin et al. Obstet Gynecol 2000 96(6)

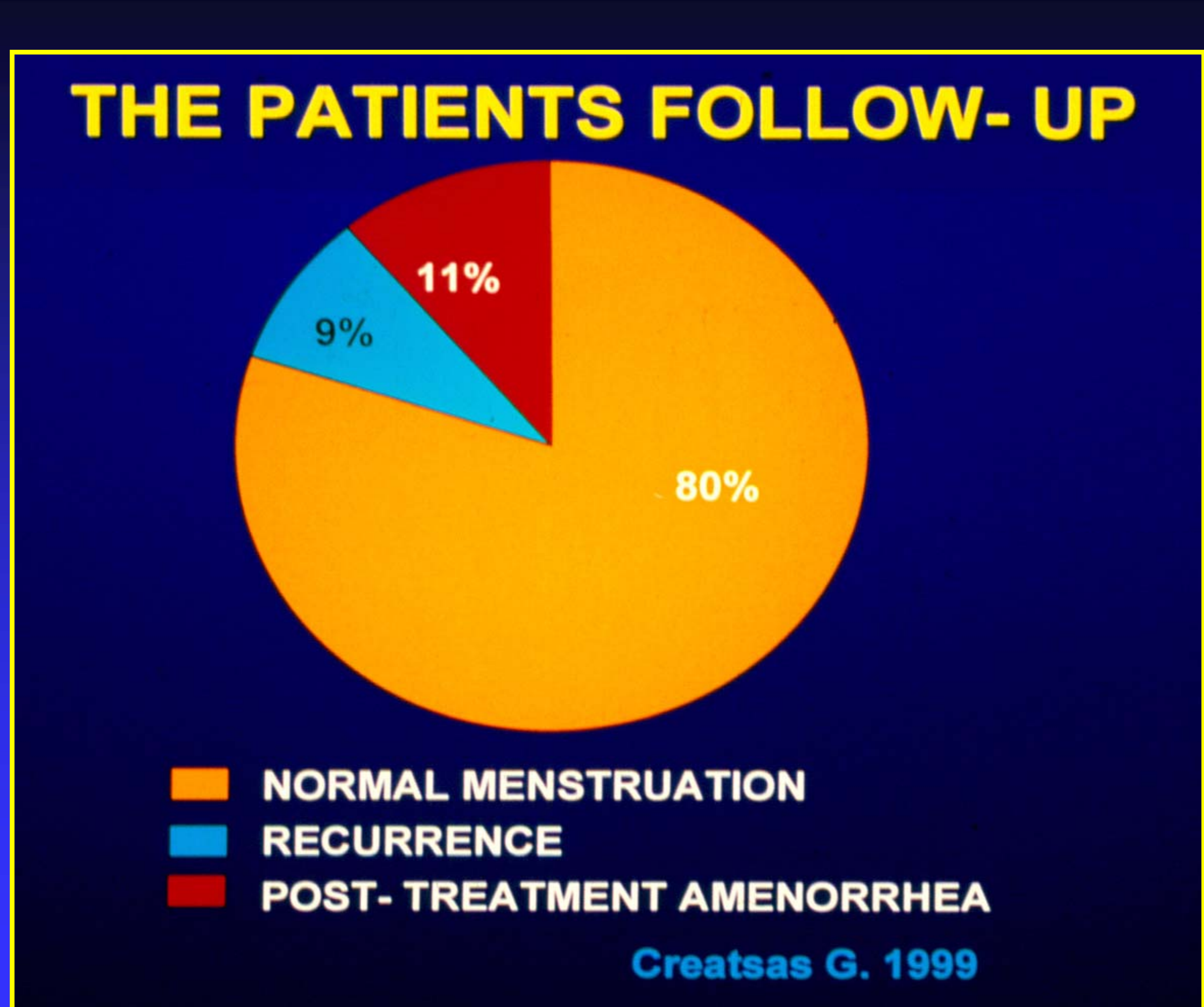
PROSTAGLANDIN SYNTHETASE INHIBITORS

REDUCE THE SYNTHESIS OF CYCLIC ENDOPEROXIDES IN THE MICROSOMAL FRACTION OF THE CELL GROWTH THROUGH THEIR INHIBITOR ACTION ON THE ENZYME **CYCLOOXYGENASE**

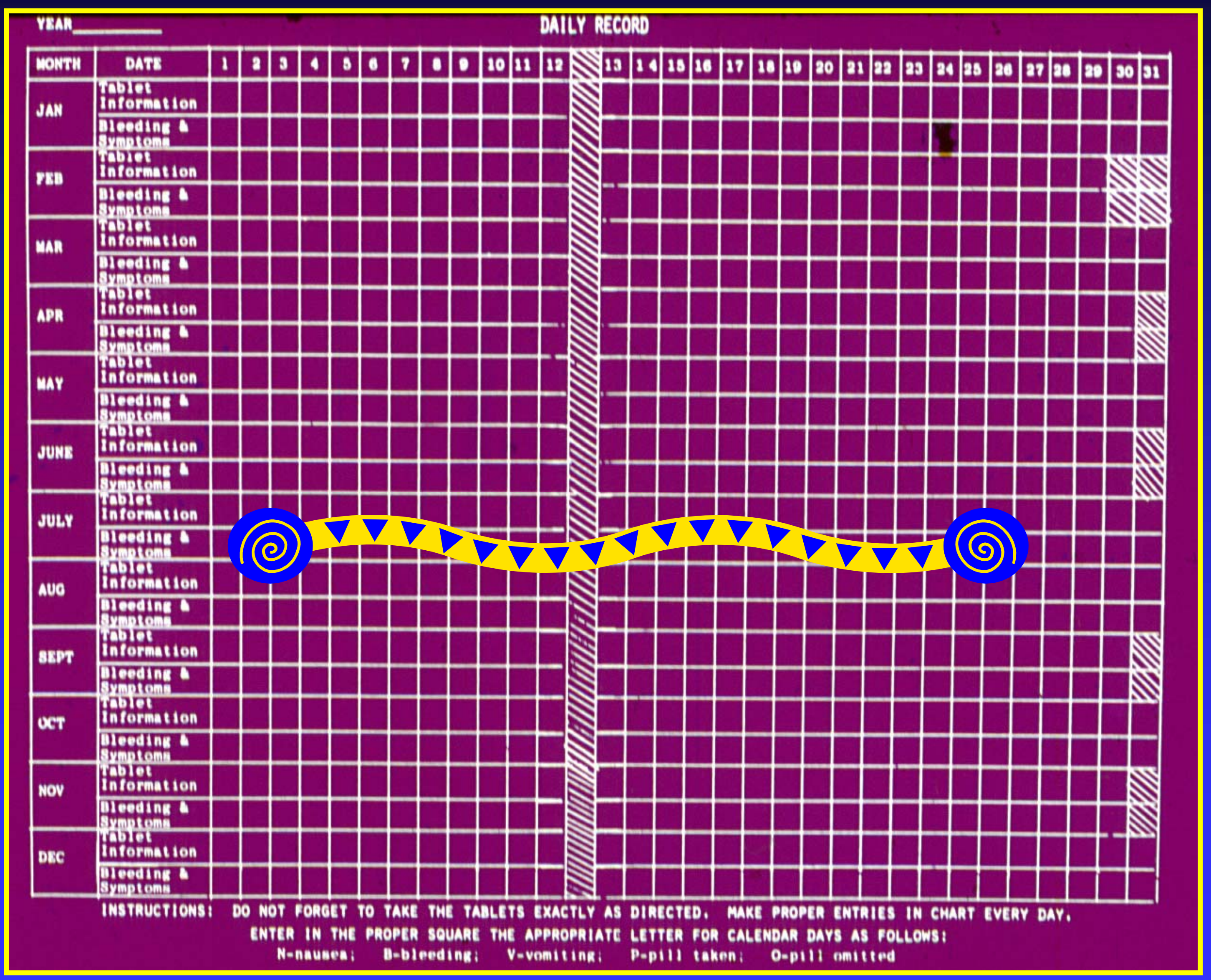
Post treatment Evaluation of Hct, Hb, and Duration of Hospitalization in Both Groups

Parameter	Tenoxicam Group (Mean±SD)	L/EE Group (Mean±SD)	P value
Hct (%)	35.9 ± 4.6	32.6 ± 4.4	0.02
Hb (g%)	11.5 ± 1.8	10.4 ± 1.5	0.05
Hospitalis..(d)	6.0 ± 2.9	8.5 ± 2.6	.001

G. Creatsas et al. Ped. Adol. Gyn 1998.


THE PATIENTS FOLLOW- UP
11%
9%
80%
NORMAL MENSTRUATION
RECURRENCE
POST- TREATMENT AMENORRHEA
Creatsas G. 1999

THE PATIENT S DIARY



YEAR________ DAILY RECORD

MONTH	DATE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
JAN	Tablet Information																															
	Bleeding & Symptoms																															
FEB	Tablet Information																															
	Bleeding & Symptoms																															
MAR	Tablet Information																															
	Bleeding & Symptoms																															
APR	Tablet Information																															
	Bleeding & Symptoms																															
MAY	Tablet Information																															
	Bleeding & Symptoms																															
JUNE	Tablet Information																															
	Bleeding & Symptoms																															
JULY	Tablet Information																															
	Bleeding & Symptoms																															
AUG	Tablet Information																															
	Bleeding & Symptoms																															
SEPT	Tablet Information																															
	Bleeding & Symptoms																															
OCT	Tablet Information																															
	Bleeding & Symptoms																															
NOV	Tablet Information																															
	Bleeding & Symptoms																															
DEC	Tablet Information																															
	Bleeding & Symptoms																															

INSTRUCTIONS: DO NOT FORGET TO TAKE THE TABLETS EXACTLY AS DIRECTED. MAKE PROPER ENTRIES IN CHART EVERY DAY.
ENTER IN THE PROPER SQUARE THE APPROPRIATE LETTER FOR CALENDAR DAYS AS FOLLOWS:
N-nausea; B-bleeding; V-vomiting; P-pill taken; O-pill omitted

ΛΕΙΤΟΥΡΓΙΚΗ ΑΙΜΟΡΡΑΓΙΑ ΤΗΣ ΜΗΤΡΑΣ ΣΤΗΝ ΕΦΗΒΕΙΑ

Γ ΚΡΕΑΤΣΑΣ MD FACS FRCOG FACOG

ΜΑΙΕΥΤΗΡΙΟ «ΜΗΤΕΡΑ»

ΑΘΗΝΑ 22 ΦΕΒΡΟΥΑΡΙΟΥ 2007