Pregnancy outcome:
is there any difference
depending on the fetal gender?

G.C. Di Renzo, MD, PhD - University of **Perugia , Italy**

The Y chromosome

The Y chromosome contains the primary sex determination gene, SRY, which has been found in all mammals , suggesting that the SRY gene is at least 130 million years old. Over time it has reduced its size by one third and contains only 50 genes

The Y chromosome

The Y chromosome is highly repetitive and mostly non-functional (probably no surprise to half of the population without one). The reason for this is that 95% of the Y chromosome never exchanges DNA with the X chromosome. In 100millions years it might disappear…

The X-chromosome represents about 5% of the total nuclear DNA and probably contains between 900 and 1200 genes, whereas the Y-chromosome contains less than 0.4% of the total DNA and contains only 78 protein-coding genes, which code for 27 distinct proteins.
(Whitehead Institute and National Library of Medicine 2004)

Early in embryonic development in females one of the two X-chromosomes is randomly and permanently inactivated, which means that females in fact are mosaics for maternally and paternally derived X-chromosomes.

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Gender aspects and ethnicity

Sex ratio (male vs female) at birth is on average 1.06

Asian or Pacific Island newborns, as a group, had the highest male/female ratio (1.06). The gender ratio for Hispanic newborns (1.04) was intermediate between non-Hispanic white newborns (1.05) and non-Hispanic black newborns (1.03). American Indian newborns had the lowest gender ratio (1.028). European studies reported a male/female ratio of approximately 1.05.

Lancet 1997

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Sex ratio related to the lenght of pregnancy

An extremely high sex ratio (male to female) was found in fetuses born after very short duration (16-19 weeks): 248:100. This ratio fell very steeply to 130:100 around the 20th week, remained almost at this level among premature births up to the 36th week, and stabilized at term around equity: 100:100.

Jongbloet, Am J Obstet Gynecol 2005

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GENDER ASPECTS

- Abortion
- Chromosomal diseases
- Fetal growth and IUGR
- Maternal diseases
- Preterm labor
- Postterm labor
- Perinatal mortality

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First trimester free beta-hCG is significantly higher in pregnancies with a female fetus

Yaron et al. Prenat Diagn. 2001

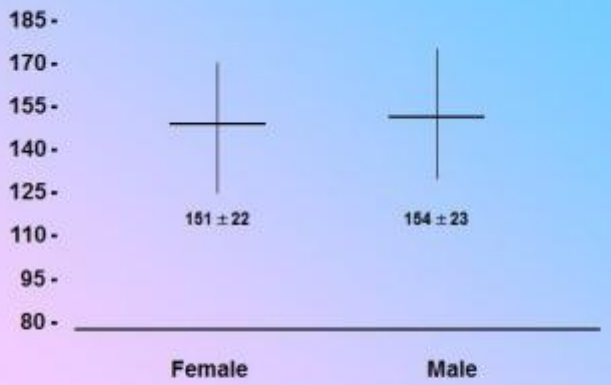
A pronounced gender impact was found for free beta-hCG, being 16% higher for female than for male fetuses.

Larsen et al., Prenat Diagn. 2002

Gender aspects of cardiovascular system

There are no significant differences between male and female FHR during the first trimester.

McKenna Fetal Diagn Ther 2006



McKenna Fetal Diagn Ther 2006

Gender aspects of spontaneous abortion

Hassold et al. estimated that the male:female sex ratio was 1.32 of chromosomally normal spontaneous abortions, i.e. a 30% increased risk for male fetuses

Ann Hum Genet 1983

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Gender aspects of aneuploidies and sonographic markers

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Markers observed in isolation or in combination by fetal sex

Marker present	Male (n=2103)	Female (n=1954)
BPD/FL>1.5 SD above normal	29 (1.4)	17 (0.9)
Cerebellum >2 SD below normal	6 (0.3)	4 (0.2)
Ear length	14(0.7)	12(0.6)
Echogenic bowel	60 (2.9)	32 (1.6)
Femur <10%	16 (0.8)	7 (0.4)
Homerus <10%	9 (0.4)	3 (0.2)
Absent middle fifth phalanx	7 (0.3)	9 (0.5)
Increased NF	16 (0.8)	8 (0.4)
Renal pelvis dilatation	**66 (3.1)**	**31 (1.6)**
ICEF	336 (16.0)	276 (14.1)
CPC	133 (6.3)	133 (6.8)
Total patients	601 (28.6)	481 (24.6)

Wax , J Ultrasound Med 2005

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Markers observed in isolation by fetal sex

Isolated marker present	Male (n=2103)	Female (n=1954)
BPD/FL>1.5 SD above normal	16 (0.8)	7 (0.4)
Cerebellum >2 SD below normal	1 (0.05)	2 (0.1)
Ear length	7 (0.3)	7 (0.4)
Echogenic bowel	35 (1.7)	29 (1.5)
Femur <10%	1 (0.05)	1 (0.05)
Homerus <10%	1 (0.05)	0
Absent middle fifth phalanx	3 (0.1)	6 (0.3)
Increased NF	8 (0.4)	2 (0.1)
Renal pelvis dilatation	**42 (2.0)**	**17 (0.9)**
ICEF	296 (14.1)	242 (12.4)
CPC	113 (5.4)	111 (5.4)
Total patients	523 (24.9)	424 (21.7)

Wax , J Ultrasound Med 2005

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Markers observed in isolation or in combination in Trisomy 21 by fetal sex

Marker	Male (n=13)	Female (n=8)
BPD/FL>1.5 SD above normal	3	2
Cerebellum >2 SD below normal	1	0
Ear length	2	0
Echogenic bowel	4	0
Femur <10%	2	0
Homerus <10%	1	0
Absent middle fifth phalanx	1	1
Increased NF	3	1
Renal pelvis dilatation	2	1
ICEF	6	3
CPC	0	0

Wax , J Ultrasound Med 2005

Female fetuses have ticker corpus callosum (CC) compare to males at any gestational age. This suggests sexual dimorphism of human CC and raises the possibility that sex hormones may play a role in callosal development

Achiron et al. , Prenat Diag 2001

Gender aspects of intrauterine infections

Amniotic fluid CMV DNA load was not significantly higher in males than in females ($p = 0.06$) and was also similar in severely and non-severely infected fetuses ($p = 0.09$).

Picone et al., Prenat Diagn. 2005

Female infants may be more susceptible to HIV infection before birth and continuing after birth. Alternatively, in utero mortality rates of HIV-infected male infants may be disproportionately higher and thus more HIV-infected female infants are born.

Taha et al., Pediatrics. 2005

22

Gender aspects of placenta previa

Demissie et al. found in a cohort analysis that the male / female ratio at birth was significantly higher in women with placenta praevia (1.19) than those without placenta praevia (1.05) ($P < 0.001$)

Am J Epidemiol 1999

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Gender aspects of preterm birth

National figures from Sweden show that boys are more likely to be delivered prematurely, accounting for 55-60% of all newborns between 23 and 32 gestational weeks. Neonatal deaths in these gestational weeks are also more common among boys. In 1993, the overall 1-year mortality rate (including all gestational weeks) in Sweden was 5.4% for boys and 4.1% for girls. The difference in infant mortality (within 1 year) is most pronounced at extremely early birth (23-24 gestational weeks) being 62% for boys compared with 38% for girls.

BJOG 2003

24

In premature deliveries at <32 weeks, male fetal gender is associated with chronic inflammatory placental lesions suggestive of a maternal immune response against the invading interstitial trophoblast.

Ghidini , BJOG. 2005

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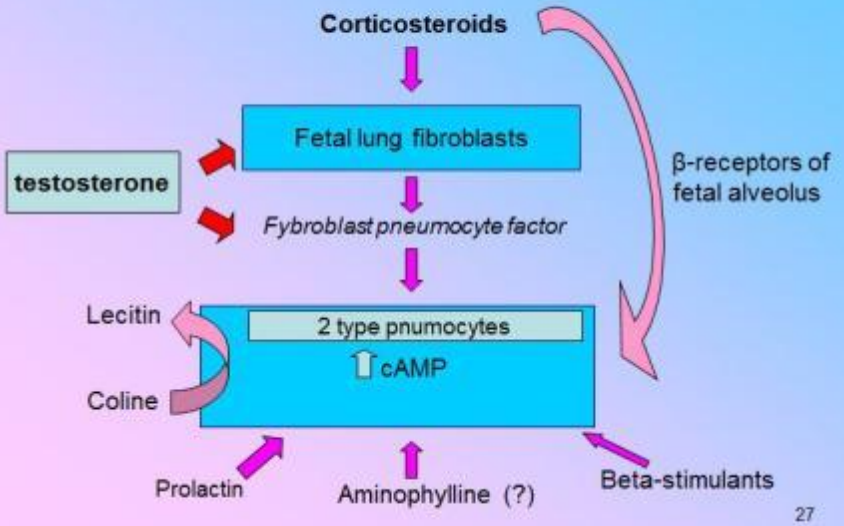
CORTICOSTEROIDS & RDS: MECHANISMS OF ACTION



Multiple logistic regression analysis to assess the independent effects of gestational age, gender, and IUGR on mortality rate, bronchopulmonary dysplasia, and intraventricular hemorrhage revealed that gestational age was the most significant contributor to all three outcome variables; IUGR contributed to an increased mortality rate, and male gender contributed to the occurrence of bronchopulmonary dysplasia.

Chen et al., J Pediatr. 1993

Gender aspects of gestational diabetes

Male group (n = 62) had higher morbidity than the female group (n = 45). This was due to a higher incidence of hypoglycemia (relative risk = 3.9, 95% CI 1.2-12.5, p = 0.011) and need to stay in the neonatal intensive care unit 2 or more days (relative risk = 1.8, 95% CI 1.1-2.9, p = 0.015). There was one female stillbirth due to an episode of ketoacidosis in the mother. Male gender (relative risk = 1.8, 95% CI 1.2-2.7, p = 0.002) was one of three independent predictors of poor outcome.

There is a male disadvantage in infants of diabetic mothers with regards to perinatal morbidity.

Bracero et al., Gynecol Obstet Invest. 1996

Gender aspects of intrauterine growth

In males, neonatal weight is mainly influenced by placental weight, maternal pre-gravid weight and weight gain during pregnancy. Males are considered more fragile than females and their production is favoured in ideal reproductive conditions, like those characterised by high maternal energy store at conception and weight gain during pregnancy.

Sexual dimorphism is due to factors, such as differences of adipose tissue composition and content, differences of leptin secretion from adipose tissue, differences of fat sensitivity to hormones (insulin, glucocorticoids), opposite effects of estrogens and androgens on leptin production, or different levels of free leptin in the circulation.

Amniotic fluid leptin levels, fetal gender and growth

	Male pregnancies	Female pregnancies	*p*
Leptin levels at 16 weeks (ng/ml)	7.89 ± 0.46	10.21 ± 0.46	0.0006
Days of gestation at term	277.5 ± 1.2	273.7 ± 1.0	0.02
Neonatal weight (g)	3487.2 ± 51.2	3253.4 ± 44.3	0.0007
Neonatal length (cm)	49.9 ± 0.3	48.9 ± 0.2	0.007
Neonatal weight/length (g/cm)	69.8 ± 6.6	66.3 ± 6.2	0.0028
Placental weight (g)	619.3 ± 16.1	591.6 ± 13.0	ns

Cagnacci et al., Eur J Ob Gin 2006

Sexual dimorphism of leptin in amniotic fluid may be of genetic origin, but may also derive from the different endocrine environment of male and female fetuses in early pregnancy. Early production of testosterone may influence production of leptin by fetal tissues and possibly impact on fetal growth.

Male fetuses with IUGR have similar outcomes when compared with female IUGR fetuses. Gender does not play a role in perinatal outcome in the setting of fetal growth restriction.

Quinones et al., Am J Obstet Gynecol. 2005

Among singleton children with cerebral palsy, abnormal intrauterine size, either small or large, is associated with more severe disability and male sex

Jarvis et al., Arch Dis Child. 2005

Gender aspects of postterm pregnancy

Male gender significantly predisposes to the prolongation of pregnancy to the extent that, by 43 weeks of gestation, there are 3 male deliveries for every 2 female deliveries.

Divon et al., Am J Obstet Gynecol. 2002

Male gender predisposes to prolongation of pregnancy

GA at birth (wks)	Odds ratio	95% CI
37	0.99	0.97-1.01
38	0.93	0.91-0.94
39	0.89	0.88-0.90
40	0.97	0.96-0.98
41	1.14	1.13-1.16
42	1.39	1.36-1.42
43	1.50	1.40-1.62

Divon et al., Am J Obstet Gynecol. 2002

Gender aspects of mode of delivery 1

Preterm females have significantly higher catecholamine levels after asphyxia than boys, which may explain the better outcome for them after a hypoxic event.

Greenough et al 1994

Gender aspects of mode of delivery 2

Dawes et al. showed that during the last hour of labour, the female fetus was associated with significantly more tachycardia (150–200 beats per minute). In contrast, the **male** fetus had significantly more bradycardia (fetal heart rate 50–119 beats per minute). One may speculate that obstetricians are more alert for interventions when bradycardia appears, which may explain the higher rate of caesarean section for fetal distress in males.

Am J Obstet Gynecol 1999

Gender aspects of fetal distress

Pronounced acidaemia (pH < 7.0) was found in 61 infants of whom 39 (64%) were male newborns, which was significantly higher than female newborns (36%). The proportion of male and female newborns within the pH range 7.0-7.04 (47 boys and 46 girls) was similar to those without acidaemia.

Ingemarsson et al BJOG 1997

GENDER ASPECTS AND PERINATAL MORTALITY

The PMR was calculated to be 113 per 1000 births. Stillbirth rate was 103 per 1000 total births; out of these, 56.5% were intrapartum and 43.3% antepartum. Male stillbirths were 89.24% in intrapartum and 62.5% in antepartum (df=1,X2=16, p < 0.001). Out of 16 early neonatal deaths, 11 were male infants. Aberdeen classification revealed obstetric causes of PMR as antepartum haemorrhage (34 cases;76% males), malpresentations (28 cases; 57% males), and congenital anomalies (26 cases; 80% males), after adjusting for maternal age and parity.

This study shows fetal gender as statistically significant risk factor for perinatal mortality.

Sami et al., J Coll Physicians Surg Pak. 2004

Stillbirth and mortality

The stillbirth rate was similar among male fetuses (3.8 per 1000) compared with female ones (3.9 per 1000). However, there was a greater than 50% increase in the number of male infants dying neonatally or within one year. In total, the rate of mortality up to one year was 3.44 per 1000 for males compared with 2.18 per 1000 for females (based on 175,382 newborns)

Sweden Nat Birth Registry 2003 42

PREGNANCY STATISTICS RELATED TO FETAL GENDER

Patients carrying male fetuses had higher rates of gestational diabetes mellitus (OR = 1.1; 95% CI 1.01-1.12; p = 0.012), fetal macrosomia (OR = 2.0; 95% CI 1.8-2.1; p < 0.001), failure to progress during the first and second stages of labor (OR = 1.2; 95% CI 1.1-1.3; p < 0.001 and OR = 1.4; 95% CI 1.3-1.5; p < 0.001, respectively), cord prolapse (OR = 1.3; 95% CI 1.1-1.6; p = 0.014), nuchal cord (OR = 1.2; 95% CI 1.1-1.2; p < 0.001) and true umbilical cord knots (OR = 1.5; 95% CI 1.3-1.7; p < 0.001). Higher rates of CS were found among male compared with female neonates (8.7 vs. 7.9%; OR = 1.1; 95% CI 1.06-1.16; p < 0.001). Using three multivariate logistic regression models and controlling for birth weight and gestational age, male gender was significantly associated with non-reassuring fetal heart rate patterns (OR = 1.5; 95% CI 1.4-1.6; p < 0.001), low Apgar scores at 5 min (OR = 1.5; 95% CI 1.3-1.8; p < 0.001) and CS (OR = 1.2; 95% CI 1.2-1.3; p < 0.001).

Sheiner et al., Fetal Diagn Ther. 2004

PERUGIA STATISTICS

MATERNITY HOSPITAL DELIVERIES
INTERVIEW TO 250 WOMEN POSTPARTUM

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Differences of perinatal outcome according to fetal gender (% on 12,000 deliveries, Perugia University Hospital) 1

	Male (%)	Female (%)	*p*<
Gestational diabetes	3.0	1.8	0.01
Preeclampsia	3.8	2.0	0.05
IUGR	3.0	4.0	0.05
Preterm birth (<32 wks)	1.7	0.9	0.05
Neon compos morbid	35.6	25.2	0.01
Malformations (excluded chromosomal)	0.7	0.4	0.05
IUFD	0.4	0.3	>0.05

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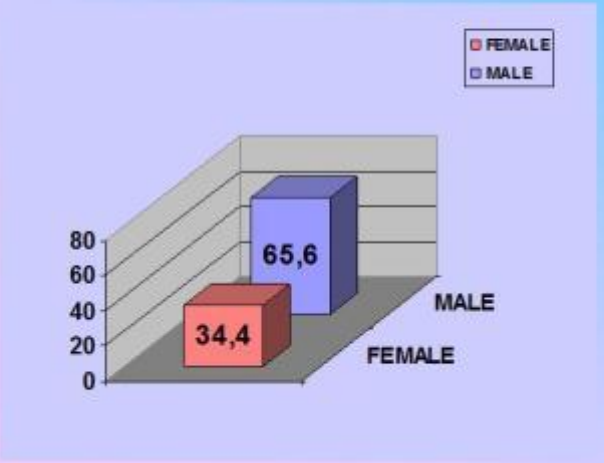
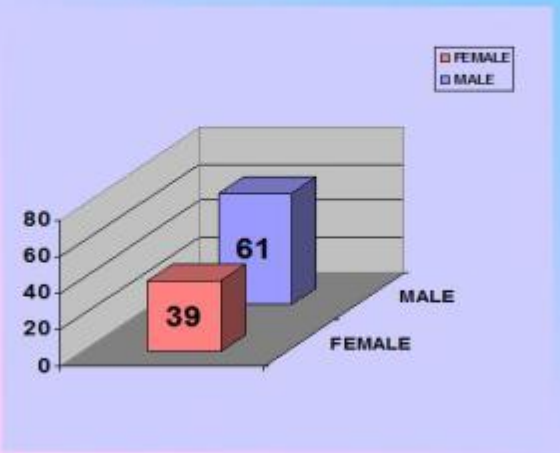
Differences of perinatal outcome according to fetal gender (% on 12,000 deliveries, Perugia University Hospital) 2

	Male (%)	Female (%)	*p*<
Cord abnormalities	2.4	0.8	0.01
Acute fetal distress	2.4	0.9	0.05
Emerg c-section	15.3	11.0	0.01

CESAREAN SECTION FOR FETAL DISTRESS

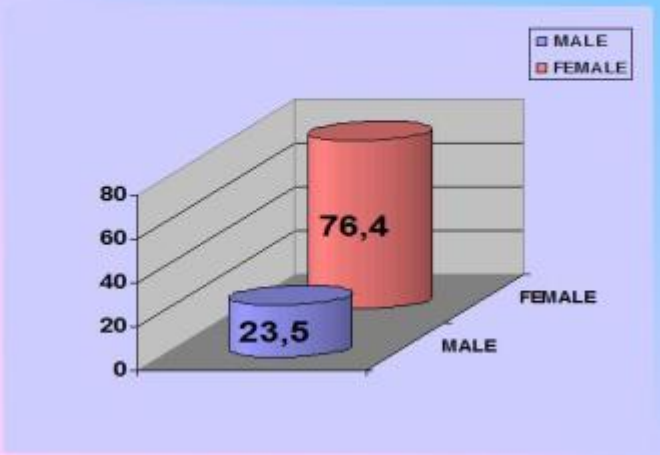


GESTATIONAL DIABETES



INTERVIEW

HYPEREMESIS GRAVIDARUM



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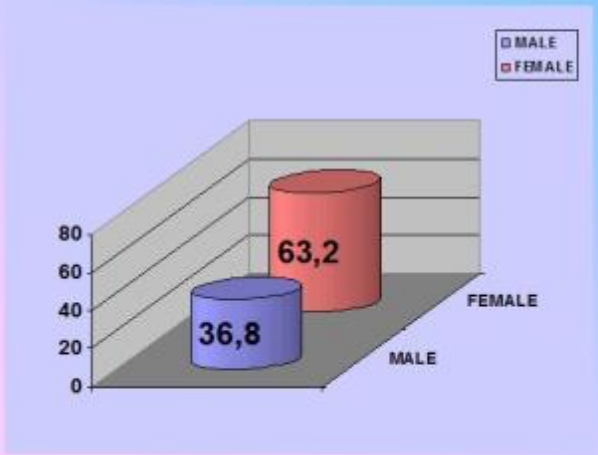
PTYALISM IN EARLY PREGNANCY



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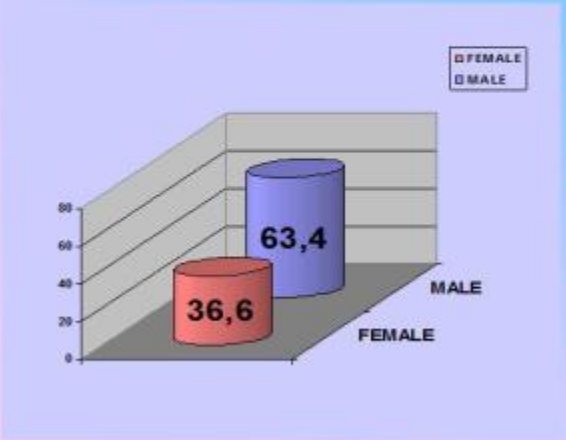
CLOASMA



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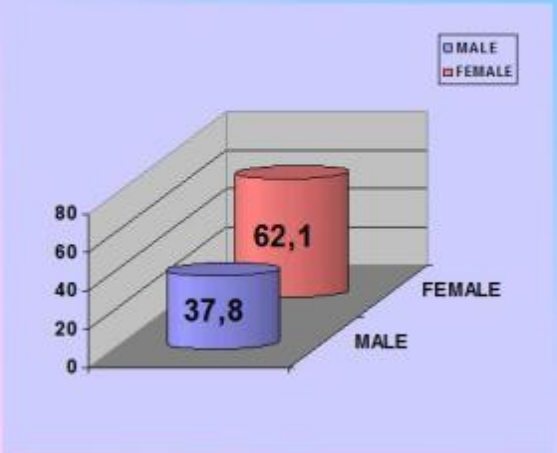
PICAS



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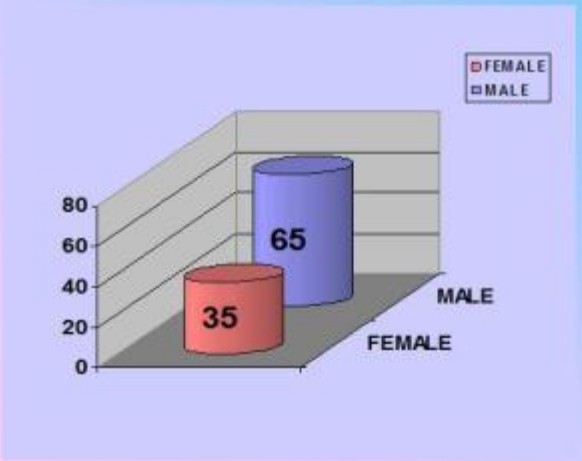
THREATENED MISCARRIAGE



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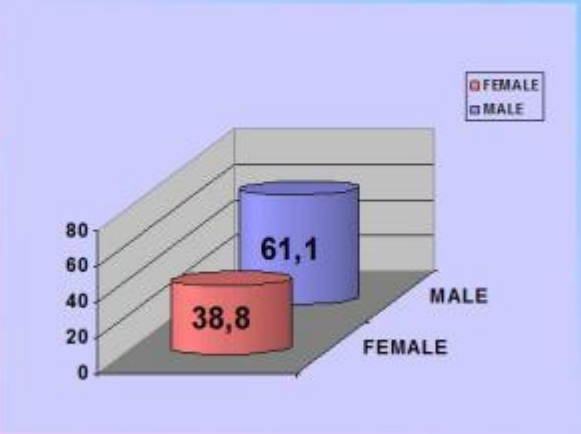
CORD AROUND NECK



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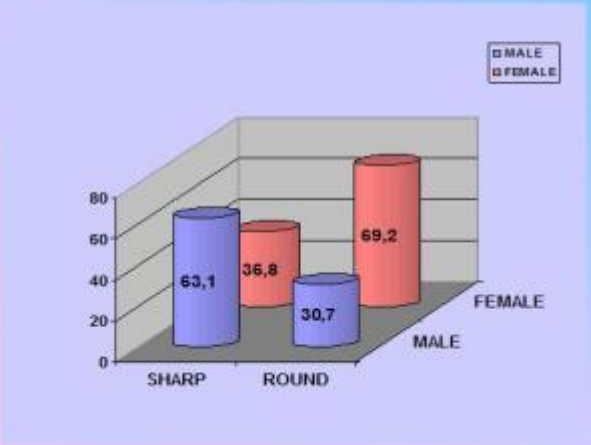
BELLY SHAPE



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DETERMINATION OF FETAL GENDER AT 10-12 WEEKS BY MATERNAL BLOOD FFDNA

True positives	180/180
True negatives	175/175
False positives	0
False negatives	0

Sensitivity %	100
Specificity %	100
PPV %	100
NPV %	100
Efficiency %	100

Di Renzo et al Am J Ob Gyn 2009

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CONCLUSIONS

There is evidence that females have an advantage over males with a better outcome in the perinatal period, particularly after preterm birth. The gender difference seems to persist throughout life, particularly regarding age-related degenerative changes in the brain. Although there are gender differences originating from the period early after conception, the exact mechanisms responsible for the continued differences later in life remain to be determined…..

Author Maureen Dowd asks if men are even necessary anymore. To add fuel to the fire, some pundits predict the death of the Y-chromosome within the next 125,000 years and believe it won't be such a devastating loss – because we'll be able to continue the human race through technology quite satisfactorily, perhaps even manufacturing people to precise and carefully determined specifications.

Dowd M. *Are men necessary? When sexes collide.* New York,NY: GP Putnam's sons; 2005:338
Sykes B. *Adam's curse: a future without men.* New York,NY: WW Norton & Co,Inc; 2006:310

The great challenge of science, though, is to look at reality as objectively as possible and not surrender to the temptation of bending the data to suit our goals, politics, or personal agendas.

Dowd M. *Are men necessary? When sexes collide.* New York,NY: GP Putnam's sons; 2005:338
Sykes B. *Adam's curse: a future without men.* New York,NY: WW Norton & Co,Inc; 2006:310

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Grazie Gracias

СПАСИБО! Thank you

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