The pattern of pregnancy loss in women with congenital uterine anomalies and recurrent miscarriage

Presented by: Kitty Huang
April 13th, 2010

Introduction

◆ Recurrent Miscarriage (RM):

  ◆ incidence rate: 1% of population

  ◆ Congenital uterine anomalies (CUA):

    ◆ in approximately 17% of the RM population (Li et al., et al., 2008).

    ◆ treatment of septate, and possibly the bicornuate uterus?

    ◆ pathogenesis?

Introduction

◆ Reports to date:

    ◆ focus:

        ◆ the reproductive outcomes of individual CUA

        ◆ investigated the effect of surgical intervention on pregnancy outcomes

Introduction

◆ 3 main limitations of reports to date:

(i) they have not all used accurate investigations (e.g. combined hysteroscopy/laparoscopy or 3-D ultrasound) to diagnose and classify CUA

(ii) they have not all studied women with RM, in which the link between CUA and pregnancy loss is more established

(iii) they have not examined the details of pregnancy loss, such as the timing of miscarriage or gestational findings on ultrasound.

Introduction

◆ The aim of this study:

- ◆ to accurately identify women with different CUA and RM

- ◆ compare the pattern of pregnancy loss with a control group of women with unexplained RM.

I Hypoplasia/agenesis
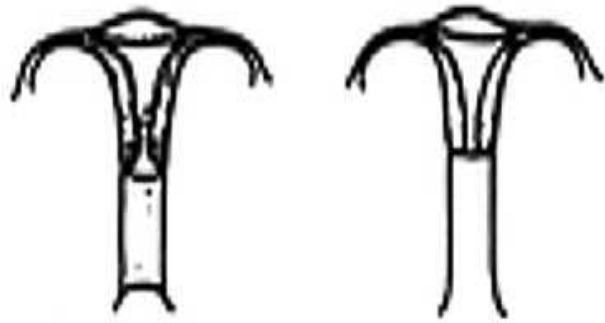
(a) Vaginal

(b) Cervical

(c) Fundal

(d) Tubal

(e) Combined

II Unicornuate

(a) Communicating

(b) Non-communicating

(c) No cavity

(d) No horn

III Didelphus

IV Bicornuate

(a) Complete

(b) Partial

V Septate

(a) Complete

(b) Partial

VI Arcuate

VII DES drug related

Materials and methods - Recruitment

- ◆ All the women included in the study attended the Sheffield Recurrent Miscarriage Clinic (Jessop Hospital, Sheffield, UK).

- ◆ Recurrent miscarriage: 3 or > consecutive pregnancy losses prior to 24 weeks of gestation.

Materials and methods -Recruitment

- ◆ All the women underwent investigations according to an established protocol (Li et al., 2002) included:
  - ◆ maternal and paternal karyotyping
  - ◆ extensive prothrombotic studies and antiphospholipid antibody screen
  - ◆ thyroid function and thyroid antibody tests
  - ◆ androgen profile (total serum testosterone, sex hormone-binding globulin and free androgen index)
  - ◆ day-2 FSH, LH and oestradiol, LH-timed Pipelle endometrial biopsy
  - ◆ screening for CUA

- ◆ A total of 665 women who completed the full investigation protocol were included in the analysis.

Materials and methods - Diagnosis of CUA

◆ A combined 2D-US and hysterosalpingography (HSG) approach.

   ◆ + finding:

      ◆ HSC/LSC procedure: to allow for a direct visualisation of internal and external uterine contour

   ◆ This provided a definitive diagnosis and classification of each anomaly.

Materials and methods - Study and control group

◆ Women with a specific CUA (diagnosed by HSC/ LSC) and no other identifiable cause of RM formed the study group (n = 56).

◆ Women whose investigations were normal for all identifiable causes of RM (unexplained RM) formed the control group (n = 107).

Materials and methods – Pregnancy outcomes

(i) biochemical miscarriage: miscarriage before week 6 of gestation or in the absence of ultrasound evidence of an intrauterine pregnancy

(ii) early first-trimester miscarriage: miscarriage after ultrasound evidence of an intrauterine gestational sac with or without a fetal pole, but prior to the presence of a fetal heart

Materials and methods - Pregnancy outcomes

◆ (iii) late first-trimester miscarriage: miscarriage in the first-trimester after the detection of a fetal heart

◆ (iv) second-trimester miscarriage: miscarriage between 14 and 24 weeks

◆ (v) stillbirth: non-viable pregnancy after 24 weeks

◆ (vi) ectopic pregnancy

◆ (vii) live birth

Materials and methods - Pregnancy outcomes

◆ Pregnancies in which patients had received medical treatment (e.g. LMW heparin, acetyl-salicylic acid, steroids) or surgery (e.g. septotomy, Strassman's metroplasty, cervical cerclage) were excluded to avoid bias in the analysis.

◆ 251 pregnancies in the study group

◆ 630 pregnancies in the control group

Results - Prevalence

◆ 665 women were screened for CUA

◆ Based on combined 2D-US and HSG imaging, the prevalence of CUA in this RM population was 13.1% (n = 87).

◆ 55 women successfully completed combined diagnostic HSC/LSC.

   ◆ 52.7% (n = 29) septate
   ◆ 32.7% (n = 18) arcuate
   ◆ 10.9% (n = 6) bicornuate
   ◆ 1.8% (n = 1) didelphys

Results - Accuracy of 2D-US and HSG

Table 1 Congenital uterine anomalies correctly detected and classified by two-dimensional ultrasound and hysterosalpingography.

Type of uterine anomaly diagnosed by combined hysteroscopy/laparoscopy	n	2D-US Anomaly detected	Correct classification	HSG Anomaly detected	Correct classification
Arcuate	18	5 (28)	0 (0)	15 (83)	7 (39)
Septate	29	8 (28)	6 (21)	23 (79)	17 (59)
Bicornuate	6	1 (17)	1 (17)	6 (100)	6 (100)
Didelphys	1	1 (100)	1 (100)	1 (100)	0 (0)
Unicornuate	1	0 (0)	0 (0)	1 (100)	1 (100)
Total	55	15 (27)	8 (15)	46 (84)	31 (56)

Values are number (%).

Results - Population characteristics

Table 2 Patient characteristics.

Patient group	n	Age (years)	Height (metres)	Weight (kg)	BMI (kg/m^2)	Cycle length (days)	Pregnancies (n)
Unexplained RM	107	31.5 ± 5.0	1.64 ± 0.1	68.1 ± 12.8	25.6 ± 5.0	28.4 ± 2.4	5.9 ± 2.3
Arcuate	18	32.9 ± 4.2	1.66 ± 0.1	68.9 ± 10.8	25.0 ± 3.5	32.5 ± 17.0[a]	6.1 ± 2.3
Septate	29	31.7 ± 5.2	1.61 ± 0.1	67.4 ± 18.0	25.4 ± 6.2	30.7 ± 12.1[a]	5.3 ± 2.1
Bicornuate	6	31.7 ± 1.9	1.64 ± 0.1	63.8 ± 10.3	22.5 ± 3.3	28.3 ± 0.5	6.2 ± 1.9
Didelphys	1	32.5 ± 0.7	1.69 ± 0.0	85.9 ± 27.1	30.1 ± 10.0	27.0 ± 1.4	6.0 ± 1.4
Unicornuate	1	21	1.6	60.3	23.6	30	7.0

Values presented as mean ± SD.

BMI = body mass index; RM = recurrent miscarriage.

Comparison to the 'unexplained RM' group. $P > 0.05$ for equality of means.

[a] $P < 0.01$ for equality of variance.

Results - Pregnancy outcome

Table 3 Pregnancy outcomes in patients with different congenital uterine anomalies.

Patient group	n	First-trimester miscarriage	Second-trimester miscarriage	Live birth	Ectopic	Stillbirth
Unexplained RM	630	431 (68.4)	21 (3.3)	152 (24.1)	19 (3.0)	7 (1.1)
Arcuate	101	74 (73.3)[a]	1 (1.0)[a]	24 (23.8)[a]	2 (2.0)[a]	0
Septate	106	77 (72.6)[a]	14 (13.2)[b]	10 (9.4)[b]	5 (4.7)[a]	0
Bicornuate	29	21 (72.4)[a]	4 (13.8)[c]	4 (13.8)[c]	0 (0.0)	0
Didelphys	10	8 (80.0)[a]	1 (10.0)[a]	0 (0.0)	1 (10.0)[a]	0
Unicornuate	5	3 (60.0)[a]	0 (0.0)	1 (20.0)[a]	1 (20.0)[a]	0

Values are number (%).

RM = recurrent miscarriage.

Comparison to the 'unexplained RM' group (2 × 2 contingency tables).

[a]Not statistically significant.

[b]$P < 0.001$.

[c]$P < 0.05$.

Results - 2nd-trimester pregnancy loss

Table 3 Pregnancy outcomes in patients with different congenital uterine anomalies.

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Values are number (%).

RM = recurrent miscarriage.

Comparison to the 'unexplained RM' group (2×2 contingency tables).

[a]Not statistically significant.

[b]$P < 0.001$.

[c]$P < 0.05$.

Results - Pattern of pregnancy loss in 1st-trimester miscarriages

Table 4 Pattern of pregnancy loss in women with first-trimester miscarriages and different congenital uterine anomalies.

Patient group	n	First-trimester miscarriages		
		Biochemical	Early	Late
Unexplained RM	263	80 (30.4)	128 (48.7)	55 (20.9)
Arcuate	42	4 (9.5)[a]	23 (54.8)[b]	15 (35.7)[c]
Septate	45	5 (11.1)[a]	26 (57.8)[b]	14 (31.1)[c]
Bicornuate	18	2 (11.1)[c]	9 (50.0)[b]	7 (38.9)[c]

Values are number (%).
Comparison to the 'unexplained RM' group (2 × 2 contingency table).
[a]$P < 0.01$.
[b]Not statistically significant.
[c]$P < 0.05$.

Discussion - Prevalence

◆ The prevalence of CUA observed in this RM population (13.1%) is slightly < the estimated prevalence in a recent review (16.7%) (Saravelos et al., 2008).

◆ The commonest CUA in this population was the septate uterus and not the arcuate uterus as previously estimated.

  ◆ the screening process of combined 2D-US and HSG is not sensitive in detecting the less pronounced arcuate
  ◆ combined HSC/LSC is not as accurate as 3D-US in detecting arcuate uteri

Discussion - Accuracy of 2-D US and HSG

◆ 2D-US detected approximately 27% (15/55) of established CUA and correctly classified about 15% (8/55).

◆ HSG detected 84% (46/55) of established CUA and correctly classified 56% (31/55).

◆ HSG is therefore better in detecting and classifying CUA, but its performance remains relatively poor.

Discussion - Accuracy of 2-D US and HSG

◆ The sensitivity of 2D-US is surprisingly low, markedly < than that estimated in the recent review (27% VS. 56%)

◆ The sensitivity of HSG is similar to the previously reported estimated (84% VS. 78%)

◆ Small septa were missed on 2D-US and that more focus was given to the HSG during the screening process.

◆ Both 2D-US and HSG are not appropriate for diagnostic purposes and should only be used as adjuncts for screening.

Discussion - Population details

◆ The characteristics of women with CUA compared with women with unexplained RM were similar in terms of age, weight, height, BMI and # of pregnancies.

◆ There was a difference in the variance of cycle length between women with an arcuate or septate uterus compared with women with unexplained RM.

   ◆ To study the endometrial morphology of arcuate and septate uteri in order to ascertain possible differences and abnormalities.

Discussion - Pregnancy outcome

- ◆ CUA have been widely reported to cause an adverse effect on pregnancy outcome.

- ◆ Pooled results suggest that the septate uterus has the worst pregnancy outcome, while the arcuate uterus has the most favourable outcome (Grimbizis et al., 2001).

  - ◆ there are some individual studies that report an opposite trend (Acie´n, 1993; Heinonen et al., 1982).

Discussion - Pregnancy outcome

◆ The results of this study suggest that the miscarriage rate ↑ according to the embryological sequence and subsequent severity of the CUA.

  ◆ women with an arcuate uterus (the less malformed uterus) have the <u>lowest rates of miscarriage</u>, which are, in fact, similar to those of women with unexplained RM (74.3% versus 71.7%).

  ◆ women with a septate or bicornuate uterus have <u>significantly ↑ miscarriage rates</u> (85.8% and 86.2%)

Discussion - 2nd-trimester pregnancy loss

◆ Studies had proved that CUA have been associated with cervical incompetence, pre-term delivery, malpresentations and ↑ C/S rates.

◆ CUA are therefore associated with 2nd-trimester losses and not 1st-trimester losses??

◆ There are very few reports that differentiate between 1st and 2nd-trimester miscarriages and that compare women with different CUA.

Discussion - 2nd-trimester pregnancy loss

◆ Woelfer et al. (2001) were the first to specifically compare early versus late miscarriage in women with different CUA.

  ◆ subseptate uteri caused more 1st-trimester miscarriages than normal uteri, while arcuate uteri caused more 2nd-trimester miscarriages.

  ◆ BUT, small # of miscarriages for women with CUA (n = 47) and no woman had a history of RM.

Discussion - 2nd-trimester pregnancy loss

◆ Proctor and Haney (2003) who found a septate uterus in 35/35 patients with recurrent 1st-trimester miscarriage and suspected CUA.

◆ However, <u>the majority of their patients were screened for CUA by HSG alone</u>, which may be less sensitive in detecting the less pronounced arcuate deformity (Saravelos et al., 2008).

Discussion - 2nd-trimester pregnancy loss

◆ Woelfer et al. (2001), the data suggest that women with a septate or bicornuate uterus have an approximate 3 x ↑ of 2nd-trimester miscarriages.

    ◆ may be related to <u>altered intrauterine pressures</u>, and <u>subsequent myometrial and cervical dysfunction</u>, which may not be of significance in the less malformed arcuate uterus.

Discussion - Pattern of pregnancy loss in 1st-trimester miscarriages

◆ This is the first study to examine the pattern of 1st-trimester pregnancy loss in women with CUA.

◆ Women with an arcuate, septate or bicornuate uterus have a similar pattern of pregnancy loss in 1st-trimester miscarriages.

◆ significantly ↓ biochemical miscarriages (<6 weeks) compared with women with unexplained RM (10.5% versus 30.4%)

◆ CUA are not associated with early implantation failure.

Discussion - Pattern of pregnancy loss in 1st-trimester miscarriages

◆ This is of particular significance in the septate uterus, which seems to behave similarly to the arcuate and bicornuate uteri.

  ◆ This implies that either implantation onto the septum does not occur readily, or if it does, it is not associated with a very early fetal loss.

  ◆ Implantation onto the septum results in a possible subfertility (Homer et al., 2000) and
  ◆ when the embryo is implanted onto the lateral walls of the septate uterus.

Discussion - Pattern of pregnancy loss in 1st-trimester miscarriages

◆ The mechanism does not cause ↑ 2nd-trimester miscarriages in the arcuate uterus.

    ◆ The pathology is less severe in the arcuate uterus
    ◆ Different mechanism causing 2nd-trimester losses in the septate or bicornuate uterus

◆ Surgical correction of the arcuate uterus does not seem indicated.

    ◆ However, there is a need for studies to assess the potential reproductive benefit of correcting the arcuate uterus.

Conclusion

◆ These findings suggest that women with a septate or bicornuate uterus, but not those with an arcuate uterus, have significantly increased rates of second-trimester miscarriages compared with women with unexplained RM.

  ◆ any woman with RM presenting with a history of a second-trimester pregnancy loss should increase the suspicion of a CUA.

Conclusion

◆ Women with an arcuate, septate or bicornuate uterus have a significantly altered pattern of 1st-trimester pregnancy loss compared with women with unexplained RM.

◆ a ↓ rate of biochemical pregnancy losses and an ↑ rate of late 1st-trimester losses.

◆ the pregnancies of women with RM and CUA are not associated with early implantation failure and are compromised at a more advanced gestational age compared with pregnancies of women with unexplained RM.