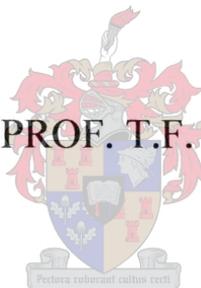


Predictive value of normal sperm morphology in intrauterine insemination (IUI): a structured literature review.

Assignment presented in partial fulfillment for the degree of masters in Medicine (Obstetrics and Gynaecology)

Promotor: PROF. T.F. KRUGER



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DECEMBER 2001

Declaration

I, the undersigned, hereby declare that the work contained in this assignment is my own original work and that it has not previously in its entirety or in part been submitted at any university for a degree.

Signature:

Date:

ABSTRACT

The aim of the study was to conduct a structured review of the literature published on the use of normal sperm morphology, as an indicator of male fertility potential in intrauterine insemination (IUI) programs. Published literature in which normal sperm morphology was used to predict pregnancy outcome in IUI during the period 1984 - 1998 was reviewed.

Four hundred and twenty one articles were identified. Eighteen provided data that could be tabulated and analyzed. Eight of the analyzed studies provided sufficient data for statistical analysis. Six studies used the Tygerberg strict criteria and two the WHO guidelines (1987, 1992). A meta-analysis of the six studies in the strict morphology group yielded a risk difference (RD) between the pregnancy rates achieved in the patients below and above the 4% strict criteria threshold of -0.07 (95% CI: -0.11 to -0.03; $p < 0.001$). WHO criteria group (1987,1992) had insufficient data to be analysed.

Meta-analysis showed a significant improvement in pregnancy rate above 4% threshold for strict criteria. Accurate evaluation of normal sperm morphology results should be an integral part of evaluating the male factor.

OPSOMMING

Die doel van die studie was om 'n gestruktureerde literatuuroorsig van die gepubliseerde data oor normale sperm morfologie uit te voer om vas te stel of dit enige waarde het as voorspeller van manlike fertiliteitspotensiaal in intra uteriene inseminasie (IUI) programme. Gepubliseerde literatuur waar normale sperm morfologie gebruik is om swangerskapsuitkoms te voorspel met IUI in die tydperk 1984 – 1998 is nagegaan.

Vierhonderd een en twintig artikels is geïdentifiseer. Agtien het genoeg data gehad om te kan tabuleer en analiseer. Agt van die geanaliseerde studies het voldoende data gehad vir statistiese analise. Ses studies het die Tygerberg streng kriteria gebruik en twee die WGO (1987, 1992) riglyne. 'n Meta-analise van die ses studies in die streng kriteria groep het 'n risiko verskil tussen swangerskapstempo in pasiënte onder en bo die 4% streng kriteria afsnypunt, van $-0,07$ (95% betroubaarheidsindeks: -0.11 tot -0.03 ; $p < 0.001$) getoon. Die WGO kriteria (1987,1992) groep het onvoldoende data gehad om te kan analiseer.

Meta-analise het 'n bekenisvolle verbetering in swangerskapuitkoms bo die 4% afsnypunt getoon vir die streng kriteria. Akkurate evaluasie van normale sperm morfologie resultate behoort 'n integrale deel te wees van die proses om die manlike faktor in infertiliteitsbehandeling volledig te evalueer.

ACKNOWLEDGEMENTS

Hereby I would like to thank the following people sincerely for their help in making this project possible and their contributions towards the successes achieved. This included:

1. Academic yearday presentation at the faculty of Medicine of the University of Stellenbosch, August 2000.
2. Ethicon Award for the best Gynaecology paper at the yearly South African Obstetrics and Gynaecology Registrars Congress, Johannesburg, July 2001.
3. Poster presentation at the Gamete to Newborn / Andrology in the Nineties Congress, Leuven, Belgium, September 2000.
4. Accepted for Publication in Human Reproduction Update, January 2001.

My promotor and mentor in the field of infertility and reproductive biology, Professor Thinus Kruger, for his guidance, support, enthusiasm and sound advice. Not only as an academic but also as a human being, he left a lasting impression on my life.

Mrs Helena Kruger for her patience and help in preparing this project for publication.

Dr Carl Lombard for his assistance with the statistical analysis.

Dr Willem Ombelet for his valuable advice and help.

All the personnel of the Reproductive Biology Unit for their help and continued support and encouragement.

Professor Hein Odendaal, head of our department, for his encouragement and support in making it possible to present these results beyond the borders of our country.

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INTRODUCTION

Intrauterine insemination (IUI) is a widely utilized method for treating distinct types of infertility. IUI is cheaper, simpler and less invasive than the more sophisticated assisted reproductive techniques of in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and gamete intrafallopian transfer (GIFT). For these reasons it is often the first line of treatment offered to infertile couples with a male factor, hostile cervical mucus, sperm antibodies or idiopathic infertility.

Sperm parameters have been correlated with success in IVF by a large number of studies but of all the semen parameters, sperm morphology has consistently been the best indicator of male fertility (Coetzee *et al.*, 1998). The main shortcomings of this parameter were the large number of classification systems used to describe which factors constitute a morphologically normal/abnormal spermatozoon and the subjective nature of the evaluation. Universally, the most common accepted classification systems used to classify sperm morphology are: World Health Organization (WHO) (1987, 1992) and Tygerberg strict criteria (Kruger *et al.*, 1986, 1988; WHO, 1999).

The aim of this study was twofold: (1) a structured literature review using medline, covering articles dealing with sperm morphology and IUI outcome published in the English language from 1984-1998, (2) the establishment of normal sperm morphology using Tygerberg strict criteria (Kruger *et al.*, 1986, 1988; WHO, 1999) and WHO guidelines (1987, 1992) as an indicator of male fertility potential in IUI programs.

METHODOLOGY

In this review, articles were found by means of computerized medline search using only the keyword “intrauterine insemination.” Limitations were English, human, 1984-1998. Reviews were also searched in the Cochrane Library using the keywords “sperm morphology and intra uterine insemination.” The databank of our infertility unit was searched by hand using the same criteria. Data was also used from the article of Montanaro-Gauci (2001). Cross references picked up during the review research were also included if they were not included initially. The searches were done by two authors (JvW/TFK) independently and results compared. Two authors were contacted to obtain data not published in order to make the analyzable data as complete as possible. Abstracts of the 421 articles sourced were evaluated and analyzed further if sperm parameters were measured against IUI outcome. Fifty one articles met this criteria. No reviews meeting our criteria were found in the Cochrane Library.

Further analysis yielded 20 articles measuring normal sperm morphology against IUI outcome. Of these articles, 18 stated a definite predictive value of normal sperm morphology but only eight articles had sufficient data to be statistically analyzed. All data that was published as pregnancy rate per cycle above and below a given/indicated threshold was included. In the study by Karabinus and Gelety (1997) pregnancy rates were documented as percentage and not as numbers which made analysis difficult. Percentages were converted to real numbers and rounded off to the lower end in both the $\leq 4\%$ and $> 4\%$ morphology groups in order to include this useful set of data. Where possible pregnancy rates where only a male factor (idiopathic) could be identified (Montanaro-Gauci *et al.*,

2001; Matorras *et al.*, 1995) were used in the meta-analysis. If the absence of female pathology was not clearly stated the pregnancy rates as given in the articles were used (whole population). Meta-analyses were conducted separately for the idiopathic and whole population groups (Matorras *et al.*, 1995 supplied data in both groups). A combined meta-analysis was done using idiopathic data where available (Montanaro-Gauci *et al.*, 2001; Matorras *et al.*, 1995) and whole population data in the balance (Toner *et al.*, 1995; Ombelet *et al.*, 1997; Karabinus and Gelety, 1997; Lindheim *et al.*, 1996; Figure 1). The statistical measure used was the risk difference (RD) between the pregnancy rates of the groups below and above the strict criteria, 4% threshold. Confidence intervals (CI) were calculated as well as probability of the chi-squared test under the null hypothesis of a zero risk difference (p-value). A random effects model (Der Simonian R and Laird N, 1986) was used that acknowledges the presence of heterogeneity. As the Tygerberg strict criteria (Kruger *et al.*, 1986,1988; WHO, 1999) and WHO criteria (1987, 1992) are the most commonly used criteria for sperm morphology in the world literature over the past few years, only articles using these criteria were analyzed.

We do not contend that this review is complete, but only that the articles reviewed constitute a representative sample of studies published on the predictive value of normal sperm morphology in the IUI situation.

RESULTS

The 18 articles that stated a definitive predictive value of normal sperm morphology were divided into a Tygerberg strict criteria group (Kruger *et al.*, 1986, 1988; WHO, 1999) and a WHO (1987, 1992) group. Of the nine articles that used the Tygerberg strict criteria (Kruger *et al.*, 1986, 1988; WHO, 1999) (Table 1), six stated a positive predictive value for sperm morphology (Montanaro-Gauci *et al.*, 2001; Ombelet *et al.*, 1997; Lindheim *et al.*, 1996; Ombelet *et al.*, 1996; Toner *et al.*, 1995; Irianni *et al.*, 1993) and three stated no predictive value at all (Schulman *et al.*, 1998; Karabinus and Gelety 1997; Matorras *et al.*, 1995) (Table I). The nine articles that used the WHO criteria (1987, 1992) for normal sperm morphology (Table II) yielded six with a positive predictive value (Chung *et al.*, 1997; Burr *et al.*, 1996; Comhaire *et al.*, 1995; Johnston *et al.*, 1994; Francavilla *et al.*, 1990; Bostofte *et al.*, 1990) and three with no predictive value at all (Tomlinson *et al.*, 1996; Milingos *et al.*, 1996; Bolton *et al.*, 1989). Eight of the papers had enough data to be statistically analyzed. Six used the Tygerberg strict criteria (Table III), and two (Tomlinson *et al.*, 1996; Burr *et al.*, 1996) the WHO criteria (1987, 1992). Using 4% as a threshold (strict criteria), results are shown in Table III.

In the strict criteria group, Montanaro-Gauci *et al.* (2001) and Lindheim *et al.* (1996) found significant differences in pregnancy rate per cycle when using 4% normal morphology as a cut off (Figure 1). A definite trend was seen towards better pregnancy rates per cycle in the >4% normal morphology group in the studies by Toner *et al.* (1995), Ombelet *et al.* (1997) and Karabinus *et al.* (1997). Matorras *et al.* (1995) found no difference in pregnancy rate in the two groups when using 4% morphology as a cut

off. Idiopathic infertility (pure male factor) was used in two of the studies (Montanaro-Gauci *et al.*, 2001; Matorras *et al.*, 1995) and whole population infertility (female factors were not clearly ruled out) in the rest of the studies (Figure 1). It must be noted that Matorras *et al.*, (1995) described data for idiopathic and whole population infertility. In his study the whole population data included the idiopathic data. A meta-analysis of the idiopathic infertility data indicated a significantly higher pregnancy rate in the >4% morphology group (Figure 1) with a risk difference (RD) of -0.084 (95% CI= -0.158 to -0.010 ; $p=0.013$) A meta-analysis of the whole population infertility data also indicated a significantly higher pregnancy rate in the >4% morphology group with a RD of -0.055 (95% CI= -0.105 to -0.006 ; $p = 0.014$). Combining these two sets of data in a meta-analysis (as described in the methodology section) a RD of -0.07 . (95% CI = -0.11 to -0.03 ; $p < 0.001$) was calculated (Figure 1).

Ovulation induction methods used in the six studies that were included in the final analysis were: Montanaro-Gauci *et al.* (2001) – mostly Clomiphene Citrate (CC), (maximum number of cycles not stated), Matorras *et al.* (1995) – Human Menopausal Gonadotrophin (hMG),(maximum number of cycles = 6), Lindheim *et al.*(1996) – hMG + hCG (Human Chorionic Gonadotrophin), (maximum number of cycles = 4), Karabinus and Gelety (1997) – CC and hMG as well as both in combination,(maximum number of cycles not stated), Ombelet *et al.* (1997) – CC and hMG, (maximum number of cycles = at least 3) and Toner *et al.* (1995) – CC as well as hMG and hMG + hCG, (maximum number of cycles not stated).

Using higher cut off values in the strict criteria group, Montanaro-Gauci *et al.* (2001) found a pregnancy rate of 11.4% (17/149) per cycle in the G-pattern group (5-14% normal morphology) compared to 24% (18/75) in the N-pattern group ($\geq 14\%$ normal morphology). Toner *et al.* (1995) had similar findings with a 7% (12/159) pregnancy rate per cycle in the G-pattern group compared to a 15% (23/150) success rate in the N-pattern group.

Using the WHO morphological evaluation (1987,1992), Burr *et al.* (1996) found no difference in pregnancy rate per cycle when 30% normal morphology was used as a cut off. The pregnancy rate in the $<30\%$ group was 16.0% (33/206) compared to 16.7% (20/120) in the $>30\%$ normal morphology group ($p=0.9121$). Tomlinson *et al.* (1996) had similar findings when using 30% normal morphology as a cut off. In their study the pregnancy rate per cycle was 21% (3/14) in the $<30\%$ morphology group compared to 20% (48/246) in the $>30\%$ morphology group ($p=1.000$). When using 10% as a cut off, Burr *et al.* (1996) found pregnancy rates of 4.3% (2/46) in the $<10\%$ morphology group and 18.2% (51/280) in the $>10\%$ morphology group ($p=0.0559$).

DISCUSSION

Petersen *et al.* (1994) studied ovulation induction with human menopausal gonadotropin (HMG) and IUI as treatment modality to compare to IVF, GIFT and ZIFT (zygote intrafallopian transfer). They found that the pregnancy rate for one cycle of HMG and IUI was inferior to IVF, GIFT or ZIFT. Two cycles were comparable to IVF or ZIFT and inferior to GIFT. Three cycles were superior to IVF or ZIFT and comparable to GIFT and four cycles were theoretically superior to all techniques. In a structured literature review by Coetzee *et al.* (1998) sperm morphology was shown to be the most useful parameter when evaluating the male factor in the IVF setting. In this review, taking all the data into consideration, an ongoing pregnancy rate of 15.2% (60/396) per cycle was calculated with morphology $\leq 4\%$. With morphology $>4\%$ an ongoing pregnancy rate of 26% (355/1368) per cycle was calculated. The findings of Petersen *et al.* (1994) and Coetzee *et al.* (1998) prompted us to evaluate sperm morphology as a predictor of pregnancy outcome in an IUI program as IUI is a none invasive procedure (no anesthetic required) and less costly than other infertility treatment modalities.

As the Tygerberg strict criteria (Kruger *et al.*, 1986,1988; WHO, 1999) and WHO criteria (1987,1992) are the most commonly used criteria for sperm morphology evaluation in the world literature over the last few years, only articles using these criteria were used in our study. In our search, 18 articles evaluated the definite predictive value of normal sperm morphology against IUI outcome. Of the nine articles that used the Tygerberg strict criteria (Table I), six stated a positive predictive value for sperm morphology. Three authors found no predictive value at all. Six of the nine articles in this group had

sufficient data to be statistically analyzed. Four of the six papers stated that sperm morphology had a positive predictive value (Montanaro-Gauci *et al.*, 2001; Toner *et al.*, 1995; Ombelet *et al.*, 1997; Lindheim *et al.*, 1996) and two stated no predictive value at all (Karabinus *et al.*, 1997; Matorras *et al.*, 1995). Our overall impression after the literature search (421 articles) is that little data was available for statistical analysis. More raw data would be very helpful in order to make a stronger conclusive statement in a study of this nature. The approach of having important data available in an article should be encouraged amongst prospective researchers/authors in the reproductive field.

The six analyzable articles were divided into two groups according to male factor infertility only (idiopathic) and whole population (if female pathology was not clearly ruled out). Idiopathic infertility was investigated separately because in the absence of female pathology the impact of sperm parameters can be studied in a better model. Matorras *et al.* (1995) were the only authors to evaluate pure male infertility as well as whole population infertility pregnancy rates after IUI. Similar trends were seen in both instances. A meta-analysis of both groups were done separately and combined eventually (Figure 1). Pregnancy rates in the idiopathic group were significantly higher in the > 4% group with a RD of -0.084 (95% CI = -0.158 to -0.010; $p=0.013$) Pregnancy rates in the whole population group were also significantly higher in the > 4% group with a RD of -0.055 (95% CI = -0.105 to -0.006; $p = 0.014$). Combining these two sets of data as described in the methodology section, an RD of -0.07 (95% CI = -0.11 to -0.03; $p < 0.001$; Figure 1) was calculated. This analysis although heterogeneous gives a clear message that the 4% threshold can be used to establish prognosis of treatment.

Although not subject to systematic review, further analysis of the analysed articles highlighted a few interesting findings. Ombelet *et al.* (1997) showed that an inseminating motile count (IMC) of $<1 \times 10^6$ was highly predictive of IUI failure if the morphology was $\leq 4\%$. No pregnancies were achieved when parameters were unfavourable. Other authors who evaluated the IMC cut off of 1×10^6 were Dodson and Haney (1991) and Hovarth *et al.* (1989). Dodson and Haney reported no pregnancies (0/17) in their study when $<1 \times 10^6$ motile sperm were used. Hovarth *et al.* (1989) reported only one pregnancy (1/38) when using $<1 \times 10^6$ motile sperm. Furthermore, success rates of IUI increased linearly when more than one follicle could be induced with follicle stimulation (Plosker *et al.*, 1994; Tomlinson *et al.*, 1996; Montanaro-Gauci *et al.*, 2001). Controlled ovarian stimulation thus always improves outcome of infertility procedures. This principle must always be kept in mind when dealing with the male factor. Other semen parameters highlighted in the articles were percentage motility where motility $>50\%$ had a three times higher success rate in IUI when compared to motility $<50\%$ with all other parameters comparable (Montanaro-Gauci *et al.*, 2001). Linearity of movement was also noted to enhance the predictive value of morphology significantly (Toner *et al.*, 1995). The findings of Montanaro-Gauci *et al.* (2001) and Toner *et al.* (1995) regarding motility and linearity of movement correlates well with the findings of Ombelet *et al.* (1997), Dodson and Haney (1991) and Hovarth *et al.* (1989) as far as IMC is concerned. All of the last three authors used standard swim-up techniques in their sperm preparation. To evaluate IMC in conjunction with sperm morphology could thus be very important to take into consideration in clinical decision making. Systematic review of the other parameters

stated should however be done before clearcut recommendations regarding the predictive value of these parameters can be made. One point of criticism on morphology evaluation is the difficulty to teach strict criteria and to get uniform consistency. Based on a recent article (Franken *et al.*, 2000) we feel confident that training followed by consistent quality control will bring uniform evaluation to clinics.

Using the WHO morphological evaluation (1987,1992), Burr *et al.* (1996) and Tomlinson *et al.* (1996) found no difference in pregnancy rates when using 30% as a morphologic cut off point. Burr *et al.* (1996) also calculated pregnancy rates using 10% morphology as a cut off. The difference was not significant (see results section), but a trend towards better pregnancy rates was seen. The 10% threshold (Burr *et al.*, 1996) for morphology, however, has a tendency towards stricter criteria. The disadvantages of the WHO (1987,1992) morphology criteria is lack of consistency and uniform threshold values by which to compare data of different authors. Threshold values (when indicated) varied from 8% (Comhaire *et al.*, 1995) to 50% (Francavilla *et al.*, 1990) (Table II). This makes the WHO (1987,1992) morphological evaluation criteria almost impossible to be practically/clinically used world-wide, even if enough raw data for statistical analysis are supplied.

Sperm morphology evaluation is an integral part of male factor evaluation. In the IUI setting, morphology (by strict criteria) proves to be a good predictor of IUI outcome. From this review we recommend that if morphology is $>4\%$, IUI should be performed irrespective of other parameters. If morphology is $\leq 4\%$ and other parameters adequate

(IMC $>1 \times 10^6$, motility $>50\%$, ≥ 2 follicles available), four IUI cycles could be performed (Burr *et al.*, 1996; Chaffkin *et al.*, 1991; Petersen *et al.*, 1994). If morphology is $\leq 4\%$, IMC $<1 \times 10^6$ and motility $<50\%$ other treatment modalities should be considered, e.g., ICSI /IVF or combined ICSI /IVF cycles. The basic semen analysis can thus be used in infertility practice to develop a cost-effective plan of treatment for the infertile couple. Although the data presented in this study is heterogeneous, the tendency to fall pregnant when sperm morphology is $\leq 4\%$ is significantly decreased especially when other factors having an impact are also unfavourable.

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Table I. Tygerberg strict criteria

Reference	Cycles	Predictive value	Thresholds
Montanaro-Gauci <i>et al</i> , 2001	495	positive	$\leq 4\%$; 5-14%; $\geq 14\%$
Schulman <i>et al</i> , 1998	544	none	No cut off indicated
Karabinus & Gelety, 1997	538	none	$\leq 4\%$; 5-9%; 10-19%; 20-29%; $> 30\%$
Ombelet <i>et al</i> , 1997	792	positive	4%
Lindheim <i>et al</i> , 1996	172	positive	4%
Ombelet <i>et al</i> , 1996	283	positive	4%
Toner <i>et al</i> , 1995	395	positive	$\leq 4\%$; 5-14%; $\geq 14\%$
Matorras <i>et al</i> , 1995	271	none	4%; 10%
Irianni <i>et al</i> , 1993	208	positive	4%

Table II. World Health Organization (1987,1992)

Reference	Cycles	Predictive value	Threshold
<i>Chung et al, 1997</i>	56	positive	No cut off indicated
<i>Burr et al, 1996</i>	330	positive	10%;11-20%;21-30%; >30%
<i>Tomlinson et al, 1996</i>	260	none	30%
<i>Milingos et al, 1996</i>	Unknown	none	No cut off indicated
<i>Comhaire et al, 1995</i>	367*	positive	8%
<i>Johnston et al, 1994</i>	10796	positive	No cut off indicated
<i>Francavilla et al, 1990</i>	441	positive	50%
<i>Bostofte et al, 1990</i>	1086	positive	No cut off indicated
<i>Bolton et al, 1989</i>	Unknown	none	40%

*Couple months

Table III: Studies with data in which 4% strict criteria threshold could be used to evaluate predictive value of normal sperm morphology (all numbers are given as pregnancy rate per cycle)

Reference	≤4%	>4%	p-value	Risk difference (95% CI)
Montanaro-Gauci <i>et al.</i> (2001)	2.6% (1/38)	15.6% (35/274)		-0.10 (-0.17, -0.04)
Toner <i>et al.</i> (1995)	7.0% (6/86)	11.3% (35/309)		-0.04 (-0.11, 0.02)
Ombelet <i>et al.</i> (1997)	12.1% (40/335)	16.5% (76/460)		-0.05 (-0.09, 0.00)
Karabinus & Gelety (1997)	6.5% (3/53)	9.0% (44/485)		-0.03 (-0.10, 0.03)
Lindheim <i>et al.</i> (1996)	1% (1/99)	19.5% (15/77)		-0.19 (-0.28, -0.09)
Matorras <i>et al.</i> (1995)	10.9% (13/120)	13.0% (3/23)		-0.02 (-0.17, 0.13)
TOTAL			<0.001	-0.07 (-0.11, -0.03)

Pregnancy rate per cycle

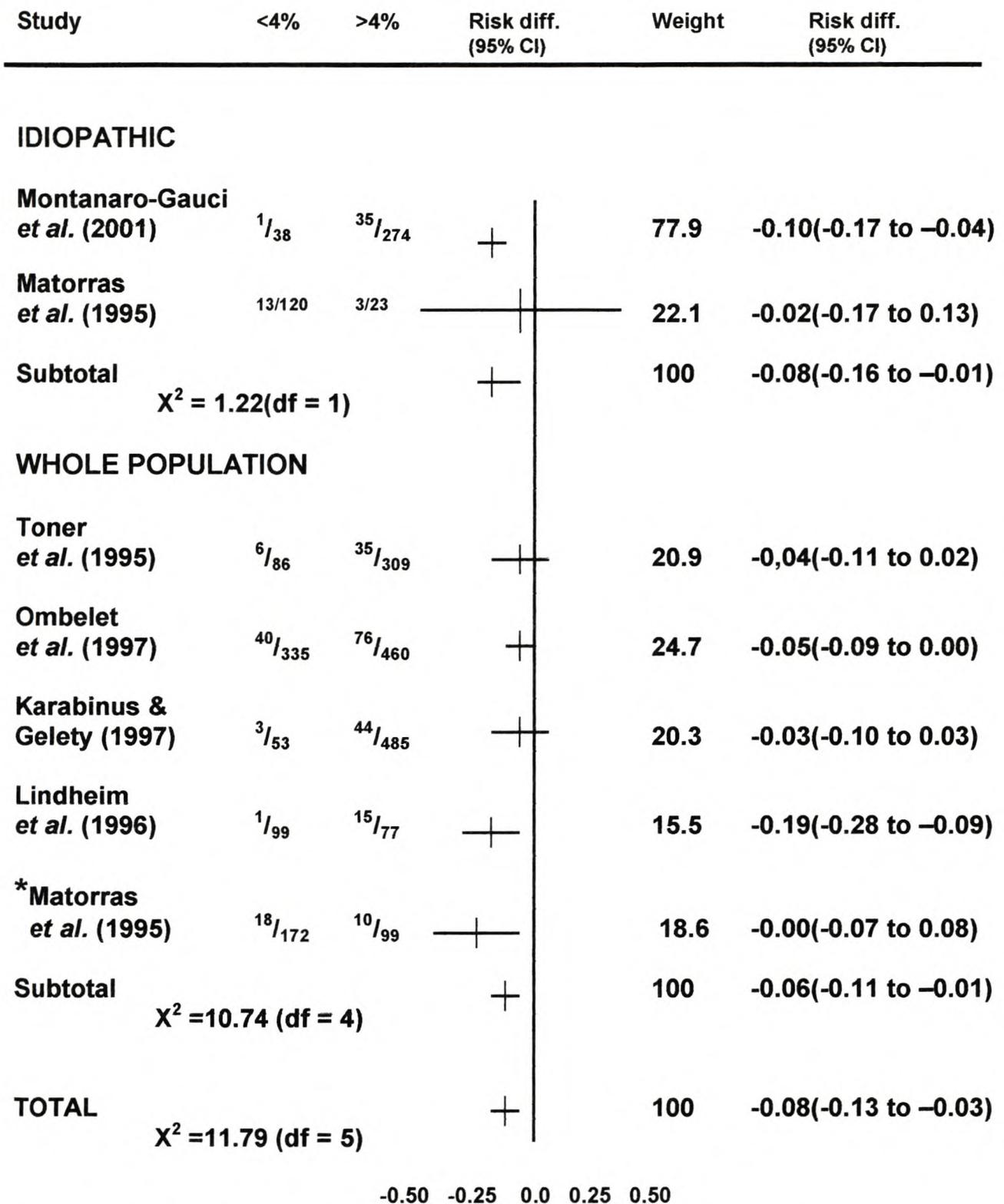


Figure 1. Risk difference for pregnancy rate (strict criteria; 4% threshold)

*Value not included (whole population) in final meta-analysis