Evaluating the Integration of Chromosomal Microarray Analysis with Karyotyping for Improved Detection of Chromosomal Abnormalities in Recurrent Pregnancy Loss: A Meta-Narrative Review

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Introduction
Investigating genetic abnormalities in recurrent pregnancy loss (RPL) is critical due to the large number of unexplained cases, which account for around 50%. While routine karyotyping of products of conception (P0C) is widely employed, its efficacy is limited by a high failure rate in cytogenetics laboratories. Thus, Chromosomal Microarray Analysis (CMA) offers a potential option, with a success rate of more than 90% when karyotyping fails. Unlike karyotyping, CMA allows a full genome investigation without the requirement for live cultures, allowing the discovery of a variety of genetic abnormalities linked to pregnancy loss, including copy number variations, deletions, duplications, and aneuploidies. These abnormalities are prevalent, representing 47.4% of first-trimester losses and 10.9% of second and third-trimester losses. Therefore, this study seeks to increase diagnostic accuracy and identify genetic variables contributing to RPL by evaluating the efficacy of combining CMA and karyotyping. This meta-narrative review serves to evaluate this combined approach as an improved method for developing individualized treatment programs and providing support to afflicted individuals and couples.

Background
RPL is characterized by the loss of three or more consecutive pregnancies at 20 weeks gestation, affecting 0.5 to 2.0% of women (Ocak et al., 2013). While half of RPL cases have unknown causes, 30 to 50% are attributed to chromosomal abnormalities (Blue et al., 2019). These abnormalities detected through Microarray analysis encompass copy number variations, deletions, duplications, and aneuploidies. Aneuploidy involves the gain or loss of a chromosome, including autosomal trisomies, monomies, and sex chromosome abnormalities (Hariapeli et al., 1985; Jia et al., 2015). Copy number changes, categorized as microdeletions or microduplications within chromosomes, may cause miscarriages, particularly larger deletions (Blue et al., 2019). Deletions entail the removal of DNA from a chromosome, while duplications involve the replication of DNA segments. CMA is a sensitive technique that offers advantages over karyotyping, including higher resolution and the ability to detect smaller mutations (Nurit Assia et al., 2015). Karyotyping, examining chromosomes under a microscope, identifies structural changes such as aneuploidy, major deletions, duplications, and other abnormalities (Giordano et al., 2019).

Methodology
The meta-narrative review method began with a thorough search using the PubMed database, focusing on the following keywords: "chromosomal microarray analysis," "karyotyping," and "recurrent pregnancy loss." Clear inclusion and exclusion criteria were established, and data extraction, comprehensive analysis, and synthesis of the results were conducted. The inclusion criteria focused on articles discussing chromosomal abnormalities and recurrent pregnancy loss, specifically the combined use of CMA and karyotyping, while the exclusion criteria excluded articles older than five years and those not directly relevant to CMA and karyotyping in the context of recurrent pregnancy loss. Data were extracted on crucial factors such as the advantages of CMA and karyotyping, the evaluation of POC samples, and the frequency of chromosomal abnormalities discovered. Through a qualitative and mixed-method process, the aim is to provide valuable insights that can contribute to advancements in the medical field and improve the quality of life for individuals affected by RPL.

Figure 1 Flow diagram of selected and excluded literatures

Results - Key Findings

- The overall detection rate for clinically significant chromosomal abnormalities in POC was 40.54%, including autosomal aneuploidy, sex chromosome aneuploidy, multiple aneuploidy, triploidy, and pathogenic copy number variants (pCNVs).
- CMA detected abnormalities at a higher rate (9.14%) compared to conventional G-band karyotyping (3.41%) in prenatual diagnosis.
- CMA exhibited a 100% success rate, higher sensitivity (90.68%), and specificity (94.40%) than karyotyping, identifying 8.9% more genetic abnormalities.
- Karyotyping had a success rate of 99.27%, with a sensitivity of 87.56% and specificity of 91.22%, remaining the gold standard for chromosomal analysis.
- Advanced maternal age correlated with increased chromosomal abnormality detection, particularly autosomal aneuploidy.
- Autosomal aneuploidy, monosomy X, autosomal trisomies, and triploidy were prevalent, especially in early pregnancy losses.
- Combining CMA and karyotyping enhanced the overall detection rate of chromosomal abnormalities.
- Routine CMA testing for POCs, especially in early first-trimester losses, is recommended, with a proposed workflow for efficiency improvement.

Figure 2 Rates of genetic abnormalities detected by CMA

Discussion
The integration of CMA with karyotyping has emerged as a highly effective strategy for detecting chromosomal abnormalities associated with RPL. CMA methods have improved detection rate, sensitivity, and specificity play a crucial role in identifying genetic abnormalities more accurately, providing crucial insights into the underlying causes of RPL. Moreover, CMA in pregnancy diagnosis. Despite this, both methods offer complementary information: while CMA excels in identifying abnormalities, karyotyping offers essential details on chromosomal abnormalities. Thus, integrating both approaches allows clinicians to overcome limitations and enhance detection accuracy, particularly in challenging cases where karyotyping alone may fail. Additionally, the combined use of CMA and karyotyping leads to better patient outcomes by improving diagnostic capacities and streamlining diagnostic procedures, especially through routine CMA testing. Therefore, this integrated strategy not only improves the diagnostic process but also leads to better patient care outcomes by providing a complete and sophisticated approach to prenatal diagnosis, ultimately enhancing patient care results in cases of recurrent pregnancy loss.

Figure 3 Web diagram illustrating the integration of CMA with karyotyping in detecting genetic abnormalities linked to RPL

Note: Data was synthesized from all four extracted Literatures

Table 1 Strengths and Limitations of the Literature Review

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<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Employed a systematic approach, ensuring thorough coverage of literature.</td>
<td>Limited generalizability due to sample limitations.</td>
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<td>Overemphasis on quantitative outcomes may neglect qualitative and clinical aspects of RPL genetic testing.</td>
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<td>Identified diverse studies, offering a range of perspectives and enriching the analysis.</td>
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Note: This diagram illustrates the synthesis of comprehensive findings regarding the integration of chromosomal microarray analysis (CMA) with karyotyping in the detection of genetic abnormalities associated with recurrent pregnancy loss (RPL).

References